Circulation

JULY 1961
VOL. XXIV NO. 1

AN OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Leopold Auenbrugger. His "Inventum Novum"—1761

IN 1761, exactly 200 years ago, Leopold Auenbrugger's *Inventum Novum ex Percussione Thoracis Humani, ut Signo, Abstrusos Interni Pectoris Morbos Detegendi,* "for detecting, by means of percussion, the obscure diseases of the chest" was first published in Vienna. It may not be without significance that his father was an innkeeper, who continually estimated the contents of casks of wine in the cellar by sounding them, and that the author himself was a musician with aural sensitivity that readily discriminated between slight changes in pitch. Auenbrugger, indeed, in his masterpiece states, "casks as long as they are empty are resonant everywhere, but when filled lose this resonance in proportion as the volume of air they contain is diminished."

The presence of fluid in the chest and in the abdomen had from time to time been recognized by succussion throughout the ages beginning with the Greeks. Percussion of the abdomen was practiced by Hippocrates for the drum-like note in tympanites—hence the name—was mentioned by him and his successors. The Hippocratic physicians in the fifth century B.C. observed a distinct splash when they shook certain patients with pleurisy, a method named succussion. The epochal contribution of Auenbrugger in "Percussion of the Chest" was, however, the first concrete description of the technic of immediate percussion on physical examination.[1-3]

Leopoldus Auenbrugger medicus viennensis

LEOPOLD AUENBRUGGER, 1722–1809

Auenbrugger was born at Gratz in Styria, Lower Austria, November 19, 1722, and received his university education in Vienna, then the center of German literature and music. Auenbrugger's interest in music was probably in part responsible for his discovery of percussion, and also led to compositions that included the libretto to Salieri's comic

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opera *The Chimney Sweep*. Sigerist[4] observed, "It would seem that he (Auenbrugger) did not shine in this domain as much as he did in the field of medicine, since otherwise he would have scarcely taken the trouble to provide a text for what Mozart (writing to his father) described as 'a pitiable work'." But his musical inclination is reflected in the first proposition of his book that states "the chest of a healthy subject sounds, when struck, like a cloth-covered drum." He evidently had a charming personality, was widely cultivated, became an intimate friend of the Empress Maria Theresa, and was designated officially as a member of the nobility. In 1751, he was appointed physician-in-chief to the Hospital of the Holy Trinity at Vienna.

The publication of "Percussion of the Chest" when he was 39 years of age was a result of 7 years' experimentation and testing of the value of the method. Auenbrugger practiced percussion with the tips of all the fingers of one hand, over a thin shirt and with a soft leather glove on his hand. He ascertained the sounds produced over healthy lungs, over collections of fluid injected into cadavers, and over various pathologic lesions in patients. The significance of the various tones elicited during life was verified by postmortem examinations. Auenbrugger, observes George Dock,[5] had two distinct tasks bound together. First, to make known the acoustic phenomena elicited by percussion of the chest and their application to diagnosis. Second, to increase knowledge of the anatomic changes in thoracic disease and their relation to percussion findings. The methodical habits of Auenbrugger are well reflected in the fact that he apparently complied with a self-imposed New Year's resolution to complete all his previous year's work by writing his "Preface" on New Year's Eve, December 31, 1760, so that his masterpiece could be published in 1761.

Of great though tangential interest is the remarkable review of "Inventum Novum" by Oliver Goldsmith, published in an English periodical August 27, 1761. This odd fragment was brought to light by the clever literary detective work of Dr. Ronald S. Crane[6] and made known to medical readers by Dr. Henry S. Viets,[7] who states "When Auenbrugger first published his book on 'Percussion,' Oliver Goldsmith was doing hack work in London for John Newbery, a bookseller in St. Paul's Churchyard. Newbery had started, in 1761, a newspaper, the 'Public Ledger,' and Goldsmith contributed papers twice a week to it. Although Goldsmith was definitely settled on his career as an author-poet, he had not forgotten his medical education and his long trip abroad which ended in a degree of M.B. from either Louvain or Padua in 1756. It is, therefore, not surprising that he was at once interested and probably appreciated the importance of Auenbrugger's discovery." In his note to the editor of the "Public Ledger," published in 1761 and discovered and republished by Professor Ronald S. Crane, Oliver Goldsmith states: "They who trust to foreign literary journals for a character of foreign publications will probably be deceived; in them we find every book well written, and every author ingenious; we must consult the works themselves if we would form a judgment.

"As I flatter myself that I shall have many of those publications, almost as soon as the journalists in question, any judgment I am capable of forming will at least be unbiased by former authority.

"There has been just published at Vienna, a Latin treatise with the following title, 'a new invention for the discovery of latent disorders in the breast, by striking the thorax; by Leopold Auenbrugger, M.D. &c.' "

Oliver Goldsmith thereupon presents an admirably concise description of the book and then he concludes, "Such are the outlines of this new discovery: whether it may be of use to society or not, there is no necessity for me to pretend to determine, only this may be observed, that the lungs are often even in the most healthy state, found to adhere to the pleura, and in such a case, I fancy the sound would, in that part, deceive the practitioners; however, I shall not pretend to set my conjecture against his experience. Upon the whole,

it is a trial that may be easily made, and to borrow an expression from Doctor Rock, *'If it cannot cure, it can do you no harm.'* ''

The ''Inventum Novum'' went through two editions but was largely ignored by the medical profession that included Auenbrugger's own teacher, the Baron van Swieten, a pupil of Boerhaave of Leyden.

It is interesting to speculate why it met with indifference or scorn. A simple method requiring no apparatus or tools but only the use of one's sensory organs, it was of great value in detecting pleurisy, empyema, and other collections of fluid. The explanation may well lie in the fact that in 1761 medicine had not progressed to the stage where the importance of accurate knowledge of structural changes in disease was recognized. Indeed, it was only in the same year that the foundation of pathologic anatomy, Morgagni's great masterpiece, *De Sedibus et Causis Morborum per Anatomen Indagatis Libri Quinque* appeared. These two books were expressions of an identical movement to establish an anatomic basis for disease and inaugurated a new era in the history of medicine. Morgagni laid the foundations of pathologic anatomy; Auenbrugger, the foundations of anatomic diagnosis. Perhaps, also, as suggested by Rolleston,[8] the conservatism responsible for opposition to Harvey's discovery delayed the acceptance of Auenbrugger's percussion. The discovery was too long before its time.

Auenbrugger's discovery did not fall entirely on barren soil, however. One of the medical periodicals of the time spoke of the ''Inventum Novum'' as a ''torch destined to illumine the darkness of thoracic disease.'' Although his immediate successors at the University in Vienna ignored the discovery, one of Auenbrugger's pupils, Stoll, later succeeded to the professorship at Vienna and testified to the great value of the method in detecting pleurisy and empyema. He also suggested its value in guiding surgical intervention. Auenbrugger in later years was accorded great acclaim. He was acknowledged to be one of the medical leaders of his time and was universally beloved and respected in Vienna.

It was not until 1808, however, when Corvisart, physician to Napoleon I, and leader of the medical profession in France, published his own observations that the value of percussion was properly recognized. He did away with the shirt and gloves of Auenbrugger but generously accorded him all credit for the method. Corvisart declared in his Preface that he was well aware of the small glory that comes to translators and to those who simply comment on the work of others. In publishing his own translation of the ''Inventum Novum,'' Corvisart stated, ''It is he and the beautiful invention which of right belongs to him that I wish to recall to life.'' The technic of percussion was then accepted but was generally practiced only later when it was related to the findings of auscultation described by Laennec. With the first English translation of the ''Inventum Novum'' by Sir John Forbes in 1824, percussion began to be widely practiced in Great Britain and the United States.

Auenbrugger lived long enough to witness the proper recognition of his work, and died at the age of 87 on May 17, 1809, 1 year after Corvisart's translation into French was published.

And so this year, as we percuss the chest to ascertain the cardiac silhouette or the nature of underlying pulmonary disease, we may take pleasure in the reminiscence of Auenbrugger and the appearance of his ''Inventum Novum'' two centuries ago. Although ''his royal gift to mankind'' of 95 pages was neglected for more than a half century, until 1 year before his death, we may reflect that ''Auenbrugger himself was too well poised and serene of nature to worry about his posthumous reputation. Grave, genial, inflexibly honest, unassuming and charitable, loving science for its own sake,'' and wholly dedicated to the welfare of his patients, he was indeed the ''compleat physician.''

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Inventum Novum

The Author's Preface

I here present the reader with a new sign which I have discovered for detecting diseases of the chest. This consists in the percussion of the human thorax, whereby, according to the character of the particular sounds thence elicited, an opinion is formed of the internal state of that cavity. In making public my discoveries respecting this matter I have been actuated neither by an itch for writing, nor a fondness for speculation, but by the desire of submitting to my brethren the fruits of seven years' observation and reflexion. In doing so, I have not been unconscious of the dangers I must encounter; since it has always been the fate of those who have illustrated or improved the arts and sciences by their discoveries to be beset by envy, malice, hatred, detraction, and calumny. This, the common lot, I have chosen to undergo; but with the determination of refusing to every one who is actuated by such motives as these all explanation of my doctrines. What I have written I have proved again and again, by the testimony of my own senses, and amid laborious and tedious exertions; still guarding, on all occasions, against the seductive influence of self-love.

And here, lest any one should imagine that this new sign has been thoroughly investigated, even as far as regards the diseases noticed in my Treatise, I think it necessary candidly to confess that there still remain many defects to be remedied—and which I expect will be remedied—by careful observation and experience.—From *On Percussion of the Chest:* being a translation of Auenbrugger's original treatise, entitled, *Inventum Novum ex Percussione Thoracis Humani, ut Signo, Abstrusos Interni Pectoris Morbos Detegendi.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 123.

A New Technic for Complete Correction of Transposition of the Great Vessels

An Experimental Study with a Preliminary Clinical Report

By F. S. IDRISS, M.D., I. R. GOLDSTEIN, M.D., L. GRANA, M.D., D. FRENCH, M.D., AND W. J. POTTS, M.D.

COMPLETE TRANSPOSITION of the great vessels is a common congenital cardiovascular anomaly. In this disease the aorta with its coronary arteries originates from the right ventricle, and the pulmonary artery arises from the left ventricle. Consequently, the aorta carries venous blood; the pulmonary artery, oxygenated blood.

Surgical correction of this malformation has been beset with many difficulties and remains a challenge to the cardiac surgeon. Many technics have been devised for its complete or partial correction.[1-12] A logical method for correcting this anomaly is retransposing the aorta and pulmonary artery. A major technical difficulty in this approach has been transfer of the coronary arteries. Obviously, if they are left in place after transplanting the major vessels, the myocardium will continue to be supplied with venous blood.

Experimental Work

From a study of autopsy heart specimens with transposition of the great vessels, the following observations were made: The right and left coronary arteries arise from the posterior sinuses of the aorta (fig. 1, nos. 3 and 4), approximately 5 to 7 mm. above the bottom of the aortic sinuses. The proximal portion of the coronary artery segments is not embedded in the myocardium as is usual in the normal heart. At their origin the coronary arteries are separated from the myocardium by a small triangular space filled with fat and areolar tissue, which facilitates their dissection.

These observations led us to develop a technic for switching the pulmonary artery and the aorta with its associated coronary arteries. This technic depends on the basic maneuver of creating an isolated aortic segment containing the ostia of both coronary arteries. This segment is then turned over and sutured proximally to the left ventricular outlet (fig. 2, nos. 6 to 8) and distally to the remaining aorta (fig. 2, no. 9).

The procedure was performed on 19 dogs with use of extracorporeal circulation. Obviously, no survivals would be expected in normal dogs when the switch-over is performed. Nevertheless, when the dogs were sustained by extracorporeal circulation at the termination of the operation their heart beats continued strong and rhythmic. The myocardium invariably remained oxygenated and pink, and the coronary circulation appeared functionally intact. Figure 3 is a roentgenogram of a dog's heart upon which the procedure was performed. The contrast material (Micropaque in gelatin solution) was injected into the aorta, demonstrating the complete filling of the coronary arteries.

The arterial switch-over was performed post mortem and in situ on several patients that died of transposition of the great vessels. Then two clinical trials were carried out.

Technic

To decrease the chances of confusion, we are giving technical details of this procedure as applied to the human heart with transposition of the great vessels. Figures 1 and 2 depict the operation as it was performed in our two clinical trials. The procedure as originally developed on dogs is slightly different from the one used in patients that is described below.

1. The chest is entered via a longitudinal sternum-splitting incision.

2. The thymus is excised and the pericardium is opened widely.

3. Umbilical tapes are placed around the superior and inferior venae cavae and the femoral artery in preparation for circulatory bypass.

4. The ascending aorta is dissected distally to the level of the ligamentum or ductus arteriosus. Proximally, the root of the aorta is freed from the fat and thin epicardium covering it.

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Aided by a grant from the Chicago Heart Association.

Dr. French was supported in this work by grant HF-10, 766 from the National Heart Institute, U. S. Public Health Service.

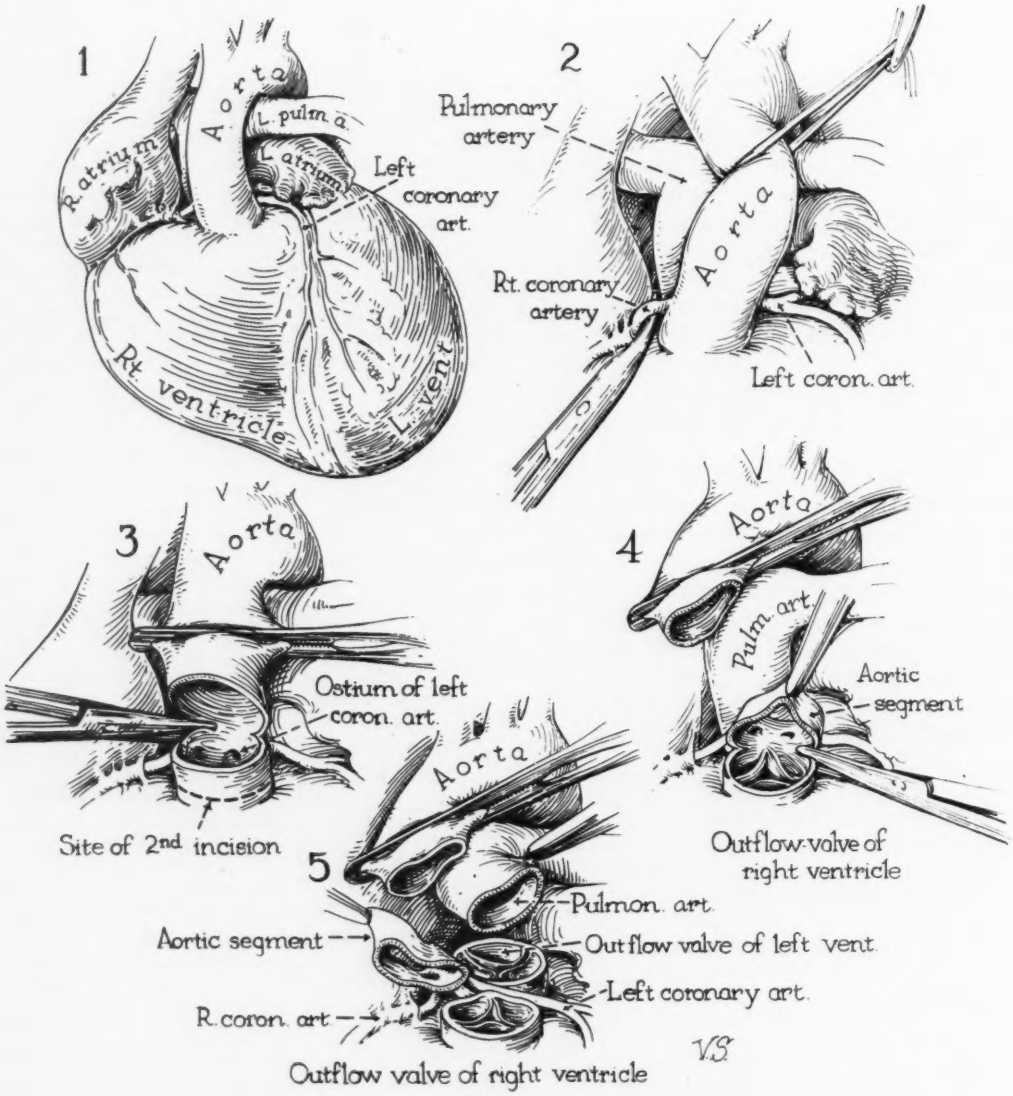

Figure 1

No. 1. External anatomy of a heart with transposition of the great vessels. No. 2. The dissection of the aorta, pulmonary artery, and left coronary artery is completed. The scissors are clearing the triangular space between the proximal portion of the right coronary artery, aorta, and myocardium. No. 3. The aortic clamp is in place and the first incision is being completed. The interrupted line demonstrates the site of the second incision. No. 4. The second incision is being completed. No. 5. The aortic segment containing both coronary ostia is shown. The segment is pulled to the right to demonstrate the outflow stumps and valves of the left and right ventricles.

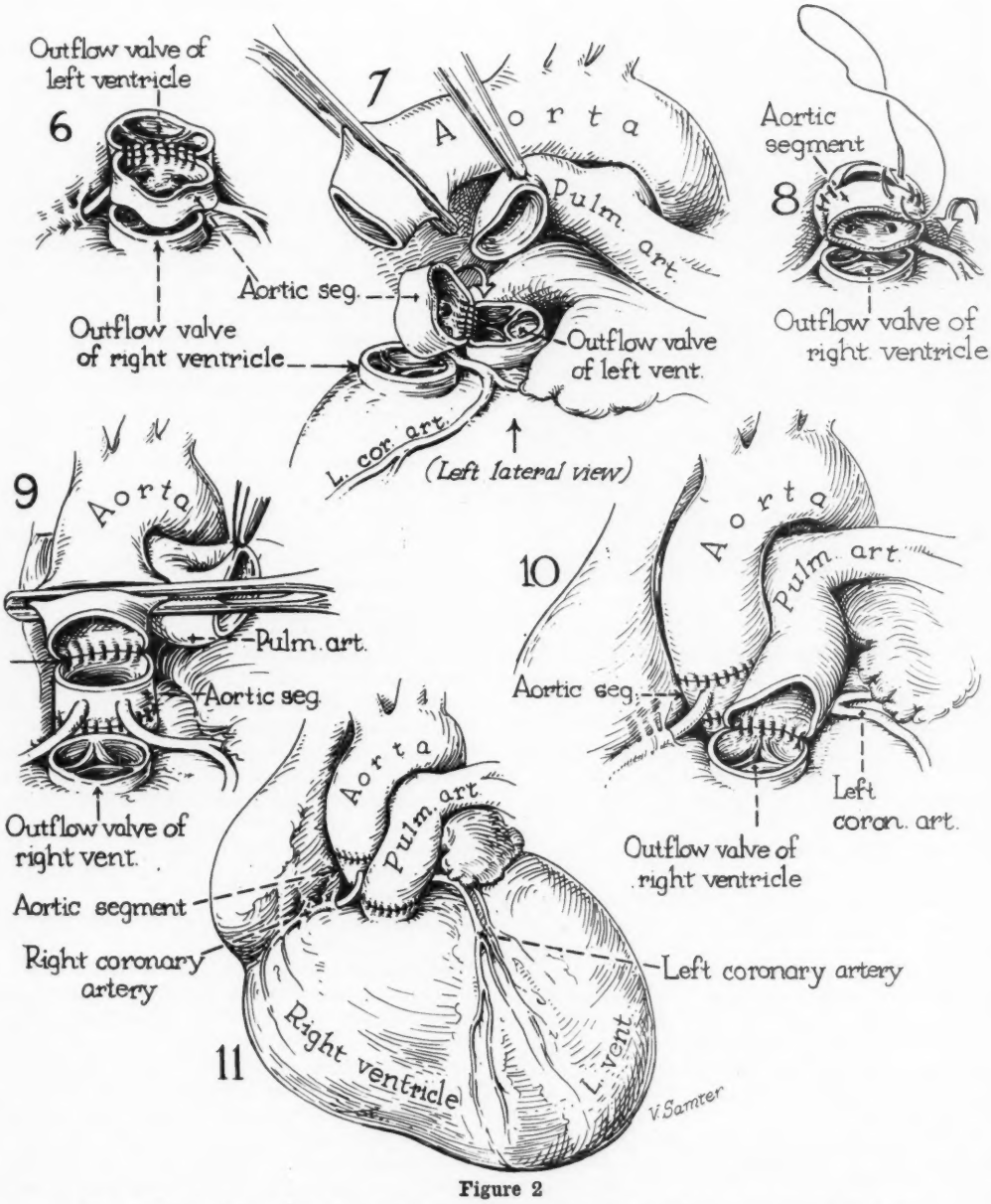

Figure 2

No. 6. *Beginning of the first anastomosis between the isolated aortic segment and the outflow stump of the left ventricle.* No. 7. *Lateral view of the heart and great vessels demonstrating how the aortic segment is turned over to fit the outflow stump of the left ventricle.* No. 8. *The first anastomosis being completed.* No. 9. *The first anastomosis completed and the second anastomosis started. Notice that the aortic segment is completely turned upside down.* No. 10. *The continuity of the systemic circuit is completed. The aortic clamp is removed. The pulmonary artery is pulled over and sutured to the outflow stump of the right ventricle.* No. 11. *The switch-over is completed.*

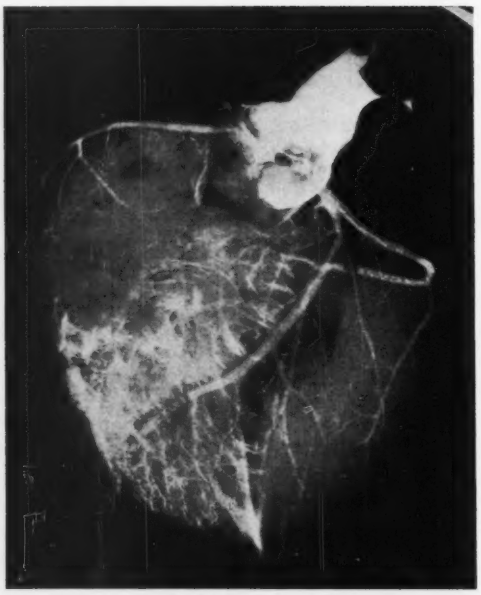

Figure 3

Complete filling of the coronary arteries is shown in this roentgenogram of a dog's heart upon which the procedure was performed. The radiopaque solution was injected into the aorta.

5. The coronary arteries are dissected free with use of a modified Potts' tenotomy scissors (fig. 1, no. 2). The arteries should not be completely denuded of their adventitia, which supports them and also carries nutrient vessels to the aortic segment.[13, 14]

6. The pulmonary artery is dissected and freed with its right and left divisions as far distally as possible. It is important to perform a thorough dissection to prevent undue tension on the suture line when the pulmonary artery is pulled over the aorta (fig. 2, no. 10).

7. After adequate heparinization, the superior and inferior venae cavae, femoral artery, and left atrium are cannulated, and extracorporeal circulation is initiated.

8. The aorta is cross-clamped with a Potts' coarctation clamp, producing ischemic myocardial arrest.

9. The aorta is transected about 5 mm. distal to the coronary ostia (fig. 1, no. 3).

10. A second transecting incision is made in the aorta proximal to the coronary ostia (fig. 1, no. 4). This incision is placed so as to leave a 3- to 4-mm. lip proximal to the coronary ostia and at the same time to preserve as much as possible of the outflow valve of the right ventricle.

This second incision completes the creation of an isolated aortic segment, containing the ostia of both coronary arteries. The average length of this segment is about 8 mm.

11. The pulmonary artery is transected about 1 mm. distal to the valve commissures (fig. 1, no. 5).

Care should be taken not to injure the valves when the pulmonary artery is transected. These valves ultimately become systemic. The length of the proximal pulmonary artery stump (outflow stump of the left ventricle) is of considerable importance. Too long a stump favors the production of regurgitation; too short a stump may injure the valve leaflets.

12. With the coronary arteries used as the axis, the aortic segment is turned over to fit the left ventricular outflow stump (fig. 2, no. 7). An anastomosis is then performed between the aortic segment and the left ventricular stump with continuous 5-0 silk suture (fig. 2, nos. 6, 7, and 8).

13. The second anastomosis is then performed between the aortic segment and the distal aorta (fig. 2, no. 9), so as to restore continuity of the systemic circuit with the left ventricle.

14. The aortic clamp is then removed, allowing the coronary arteries to be perfused and the heart to resume contractions. The duration of anoxic arrest is limited to an average of 30 to 35 minutes.

Because of heparinization, bleeding from the anastomotic site is a major problem. Meticulous placement of the sutures helps to prevent excessive bleeding. Gelfoam moistened with topical bovine thrombin placed over the suture line aids in stopping bleeding from needle holes. When bleeding is excessive, thrombin is washed out and becomes ineffective. We found it advantageous to cross-clamp the aorta for 2 to 3 minutes so that clotting may occur.

15. The pulmonary artery is anastomosed to the outflow stump of the right ventricle (fig. 2, no. 10), to complete the switch-over (fig. 2, no. 11).

16. Circulatory bypass is stopped.

Due to the anatomic differences between the dog's heart with normal outflow tracts and the human heart with transposition of the great vessels, the procedure described above is slightly different from the one originally developed on dogs. The coronary arteries of the normal dog's heart are embedded in the myocardium. They are more difficult to dissect than in the human heart with transposition of the great vessels. Furthermore, the left coronary artery is covered by the pulmonary artery. We found it advantageous in dogs to perform as much as possible of the dissection and then to start bypass and transect the pulmonary artery. This maneuver facilitates the exposure and the completion of the dissection of the left coronary artery.

Regurgitation was a frequent occurrence after completion of the switch-over in dogs. A single suture placed as shown in figure 4 helps to control any valvular insufficiency. Regurgitation was not encountered in the clinical trials.

Case Reports

Two patients with transposition of the great vessels were operated upon at The Children's Memorial Hospital in Chicago with use of this procedure.

Case 1

J. S. was a 7-year-old white boy with severe cyanosis since birth and severe clubbing of the digits. Clinical diagnosis of transposition of the great vessels was made soon after birth. Six months prior to surgery there was progressive clinical deterioration with decreasing exercise tolerance. Cardiac catheterization then confirmed the diagnosis of transposition. A bidirectional shunt at the atrial level and an intact ventricular septum were found. The pressure in the right ventricle was 108/8 mm. Hg, in the aorta 108/80 mm. Hg, in the left ventricle 37/8 mm. Hg, and in the pulmonary artery 37/15 mm. Hg. The arterial saturation was 69 per cent. The estimated pulmonary blood flow was 7.4 L./M.^{2}/minute and the systemic blood flow 5.9 L./M.^{2}/minute. The electrocardiogram demonstrated right ventricular and right atrial hypertrophy. The chest roentgenogram showed cardiac enlargement and increased pulmonary vascularity. A cineangiocardiogram corroborated the diagnosis of transposition of the great vessels.

After adequate digitalization, the operative procedure described was performed on June 29, 1960.

After the continuity of the aorta with the left ventricle was established, the aortic clamp was removed and the heart resumed its beats spontaneously. The heart contractions were strong and rhythmic, and the myocardium was uniformly pink. The electrocardiogram showed no evidence of coronary insufficiency at that time. The pulmonary artery anastomosis was then performed, and the interatrial septal defect was closed with a continuous suture through a right atriotomy.

The extracorporeal circulation was then stopped. The heart continued normal contractions for a few minutes, then started to slow down and the left ventricle became markedly distended. Cardiopulmonary bypass was resumed, and the heart rate increased and the cardiac contractions again became vigorous. There was no evidence of aortic valve regurgitation. Stopping and resuming bypass several times reproduced the same sequence of events; good cardiac contractions resulted on bypass, and weakening of the contractions with left ventricular dilatation occurred when off bypass.

Figure 4

Suture placed in the myocardium of the right ventricle in dog at the completion of the operation to prevent herniation of the valves with the production of regurgitation.

The sutured interatrial defect was reopened with the hope that it would decompress the left side of the heart, but to no avail. The patient died of acute left ventricular dilatation and failure. Postmortem examination showed a thin-walled and dilated left ventricle. The right ventricular wall was markedly hypertrophied, three times the thickness of the left ventricular wall. The coronary arteries and ostia were patent to probing.

Comment

In retrospect, this patient may not have been a suitable candidate for this procedure. The age and size of this patient and his general satisfactory condition coupled with the fact that he had an intact ventricular septum were strong factors in our choice. Although the left ventricular pressure was low, it was anticipated that the left ventricular myocardium could support the pressure postoperatively, since it had been carrying a considerably increased flow load. We now think that for this type of procedure, the left ventricular pressure should approximate or equal the right ventricular pressure.

Case 2

M. B. was a 3½-month-old white girl, cyanotic since birth. The diagnosis of transposition of the great vessels was considered clinically, and it was then confirmed by cineangiocardiogram and cardiac catheterization. A left-to-right shunt at the atrial level, a patent ductus arteriosus, and an intact interventricular septum were found. The left ventricular pressure was 52/0 to 5 mm. Hg, the right ventricular pressure 62/5 mm. Hg, the aortic pressure 62/38 mm. Hg. The arterial saturation was

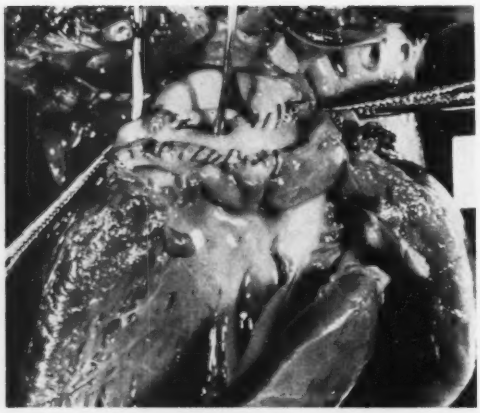

Figure 5

Postmortem specimen of case 2 showing a view of the left ventricle in continuity with the aortic segment and aorta. The two aortic suture lines are seen. Two probes point to the coronary ostia.

67 per cent. Chest roentgenogram showed 2+ cardiac enlargement and increased pulmonary vascularity.

The operation was performed on August 17, 1960, and the procedure as described above was done. Since this patient was an infant, we thought that we should interrupt the suture line at several points in the anastomosis to prevent any interference with the circumferential growth of the major vessels. At the completion of the second anastomosis, the aortic clamp was removed and the heart resumed its beats spontaneously. Excessive bleeding from the anastomosis compelled us to reclamp the aorta and try to control the bleeding. We also elected to perform the pulmonary artery anastomosis at this time while we had a dry field. The aortic clamp was removed and again the heart resumed its beats. Bleeding from the anastomotic sites continued to be excessive and could not be controlled. Although Gelfoam soaked in topical bovine thrombin had previously been very effective in controlling bleeding, it did not have any clotting effect in this case.

A vicious circle resulted from the bleeding. The pump had to be transfused rapidly with large amounts of cold blood. This dropped the temperature of the infant to 29 C. Since we were using a radiant heating unit against the oxygenator, warming of the blood was not sufficiently effective.

Circulatory bypass was stopped, and protamine sulfate was given intravenously but it did not control the bleeding. The heart rate was slow from the effect of cooling. The left ventricle showed no sign of dilatation. The bleeding continued, the aorta became flabby, and the patient died from acute blood loss. Postmortem examination showed the right and left ventricles to be of almost equal size. The coronary ostia and arteries were patent to probing. Figure 5 shows a view of the left ventricle with the outflow tract in the postmortem specimen. Two probes indicate the coronary ostia.

Comment

In this case, bleeding appeared to be the cause of failure.

Discussion

This work demonstrates that switching the pulmonary artery and aorta with both coronary arteries is technically feasible and appears to be practical in correcting transposition of the great vessels. The basic features that make it possible to transfer both coronary arteries with the aorta are the intact circular aortic segment and the "turning over" maneuver. The intact aortic segment acts in reality as a graft lengthening the coronary arteries. This lengthening obviates the difficulty associated with the individual transfer of the small coronary arteries. Since the coronary ostia in transposition of the great vessels are usually on the side of the aorta adjacent to the pulmonary artery, the only way to transfer this segment of the aorta containing both coronary arteries is by turning the segment over to fit the outflow stump of the left ventricle. This maneuver does not interfere with coronary circulation. Adequacy of the coronary circulation was demonstrated by the uniform presence of good heart action in the dog experiments and the roentgenogram of the postoperative injection study of a dog's heart (fig. 3). The experience with the clinical trials further demonstrates sufficiency of the coronary circulation as evidenced by good filling of the coronary arteries, the uniformly oxygenated myocardium, the strong myocardial contractions, and the absence of coronary insufficiency pattern in the electrocardiogram during the bypass.

Our experience with the first case demonstrates the importance of patient selection. This first patient died because the left ventricle was unable to handle the sudden load imposed on it. A left ventricle adequate to cope with a work load comparable to that pre-

sented by the systemic circuit seems to be a prerequisite to the success of this operation. Young infants with equally developed right and left ventricles and older children with associated ventricular septal defects and high left ventricular pressure would probably be the best candidates for the arterial switching procedures.

A high percentage of children with transposition of the great vessels succumb in the first few months of life. Many of them are without associated ventricular septal defects. We think that this operation may provide the best opportunity for salvage of such infants.

The question of repairing associated defects at the time of arterial correction remains to be answered. Patent ductus arteriosus must be closed and preferably divided and sutured to permit complete mobilization of the pulmonary artery. We do not plan now to close the ventricular septal defects in subsequent cases.

Summary

A procedure for complete anatomic correction of transposition of the great vessels is described. The technic is based on the concept of isolating an aortic segment containing both coronary ostia and turning the segment over to fit the outflow stump of the left ventricle. Experimental work and two clinical trials are presented and discussed.

We believe that this operation provides an anatomic and physiologic correction of the great vessels and coronary arteries in transposition. In spite of two clinical failures, we think this operation is worthy of further trials.

Acknowledgment

We wish to thank Dr. W. Riker, Attending Surgeon; Dr. R. Miller, Chief of Cardiology; and Dr. M. H. Paul, Head of the Cardiovascular Laboratories, at The Children's Memorial Hospital of Chicago for their assistance and advice in this work.

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A-V Nodal Tachycardia with Block

By ALFRED PICK, M.D., RICHARD LANGENDORF, M.D., AND LOUIS N. KATZ, M.D.

MYOCARDIAL FIBERS at the atrioventricular junction, specialized by virtue of morphologic features and bioelectrical behavior,[1] have the property of transmitting impulses as well as creating them. In keeping with this double function, pathologic states in this area are manifested in clinical electrocardiograms in two ways: 1. Undue prolongation of refractoriness to stimulation, at one or several junctional levels, may lead to retardation or failure of impulse conduction in a forward or retrograde direction, or both; the result is atrioventricular (A-V) block of various degrees. 2. Spontaneous impulse generation, ordinarily subsidiary, may become enhanced in a paroxysmal or nonparoxysmal manner; this results either in domination of the entire heart by the rapid ectopic impulses or in various types of A-V dissociation.[2] These two functional disorders may develop independently, simultaneously, or one may follow in the wake of the other. Nonparoxysmal A-V nodal tachycardia, without or with A-V block, and its clinical significance were the subject of a previous communication.[3]

The present report deals with further observations on A-V nodal tachycardia associated with conduction disorders. In the majority of cases, the nodal acceleration was nonparoxysmal in type and attributable to digitalis therapy—probably carried to excess. Simultaneous spread of the impulse to the atria and ventricles, or restriction of impulse propagation to one direction, precluded direct measurements of forward and retrograde A-V conduction times of the rapid nodal impulses. However, the presence and type of the associated conduction disorders in the A-V junction or in the ventricles could be established on the basis of the characteristic arrangement in the irregular beating of the atria or ventricles or from the type of aberration in ventricular impulse propagation. Of 27 observations in this category we selected eight for illustration, each with a particular diagnostic aspect; some also carried practical implications with regard to digitalis therapy. For systematic presentation these cases are arranged under five headings on the basis of the mode of atrial activation, the simultaneous action of more than one nodal pacemaker, and the different locations in which a conduction disorder may develop under such circumstances. The distribution of these five types among the 27 cases studied is listed in table 1. However, since we only recently learned to recognize nodal tachycardia with block in the presence of atrial fibrillation, its frequency in our electrocardiographic files may actually be much higher than indicated in the table.

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Aided by the Michael Reese Research Foundation and the Oppenheimer Fund for Cardiovascular Research.

Presented in part at the Thirty-third Annual Meeting of the American Heart Association, St. Louis, Missouri, October 1960.

The Material and Its Interpretation

I. A-V Nodal Tachycardia with Block in the Presence of Atrial Fibrillation

Figure 1 is a tracing of a 70-year-old man with arteriosclerotic heart disease and atrial fibrillation, chronically digitalized. This is revealed by the tiny undulations in lead II. It was seen in many records (37) over a period of 4 years, taken before and after the record shown. In the first part of the continuous lead (upper strip) the ventricular action is precisely regular at a rate of 125; in the second part (lower strip) it is completely irregular but with the following particular pattern (table 2): (1) there are groups of two to six faster beats separated by pauses; (2) within the longer runs of faster beats the cycle progressively shortens so that (3) after 3 or more beats the last cycle before a pause is always shorter than the first cycle following the pause; (4) the pauses measure less than the sum of two consecutive short cycles. This, then, is the characteristic structure of a ventricular arrhythmia developing as a consequence of a

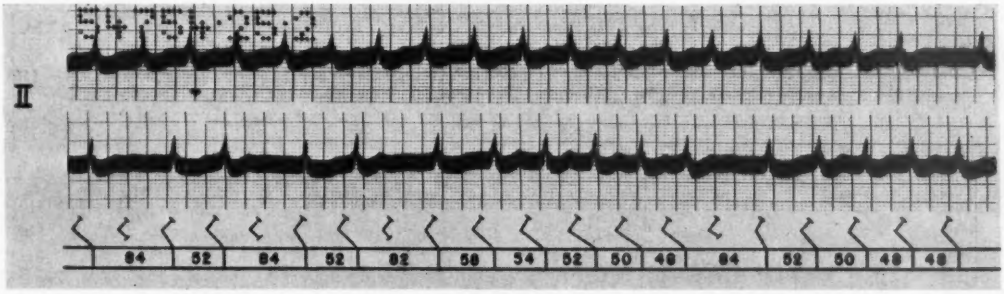

Figure 1

Nonparoxysmal A-V nodal tachycardia with second-degree A-V block in the presence of atrial fibrillation and complete A-V dissociation. Continuous long lead II. The last cycle of the upper strip is reproduced as first cycle in the lower strip.

second-degree A-V block with Wenckebach periods.[4, 5] On the basis of these measurements, the following uniform interpretation of the entire record was derived and indicated diagrammatically for the lower strip:

Complete A-V dissociation is present throughout. It is induced by the accelerated activity of a regular A-V nodal pacemaker. The retrograde impulses from this latter pacemaker cannot enter the atria but keep the region above the pacemaker in a constant state of refractoriness so that none of the rapid atrial impulses reaches the nodal pacemaker. In the first portion of the record with regular beating, all nodal impulses activate the ventricles (and are transmitted at a constant conduction speed); later, one out of three, or one out of seven, consecutive nodal impulses fails to do so following progressive retardation of conduction through the lower part of the A-V junction. The 3:2 conduction ratio at the beginning of the lower strip causes a transient ventricular bigeminy (cf. fig. 2).

A similar approach can be used in interpreting the ventricular arrhythmia present in figure 2, a tracing obtained in a 67-year-old woman with rheumatic and arteriosclerotic heart disease who was receiving digitalis medication. Atrial fibrillation is present,* with repetitive arrangement of ventricular beats in groups of two or three. Throughout leads I and II, and at the start of lead III, all short cycles are constant (0.48 second) and long ones reveal only slight variation (0.74 to 0.76 second). Furthermore, whenever a short cycle follows a longer one, the QRS

*This was clearly seen in right precordial leads which also permitted the ruling out of atrial flutter. Atrial fibrillation was present in all seven records taken on this patient in 4 months, before and after the record shown in figure 2.

Table 1

Distribution of the Various Types of A-V Nodal Tachycardia with Block in the Material Analyzed

A-V n. t.* with block in the presence of					
Atrial fibrillation†	Sinus rhythm†	Retrograde conduction	Double A-V n. t.†	"Bidirectional" A-V n. t.*	Total
10	1	6	5	5	27

*A-V n. t. = A-V nodal tachycardia.
†With A-V dissociation.

is smaller, more slurred, and slightly widened (0.12 second), and the T wave is larger. This consistent variation in spacing and contour could suggest that ventricular premature ectopic beats are responsible for the grouping. In the middle of lead III (ninth to fourteenth beat), however, this spacing pattern is disturbed and with it the difference in contour disappears. This provides the clue to a more appropriate interpretation of the entire record indicated in the diagram.

Thus, in this case complete A-V dissociation has been engendered in the presence of atrial fibrillation by the acceleration of A-V nodal impulse formation to a rate of about 150 per minute (cycle length $= \frac{0.48 + 0.74 \text{ second})}{3}$.

Every third or fourth of the *regular* nodal impulses is blocked in the lower A-V junction resulting in ventricular (pseudo-) bigeminy and trigeminy, respectively. In successively conducted nodal impulses the conduction time to the ventricles lengthens progressively (Wenckebach phenomenon), but not always to the same extent. With small increments the ensuing ventricular cycle remains short (0.48 second) and, hence,

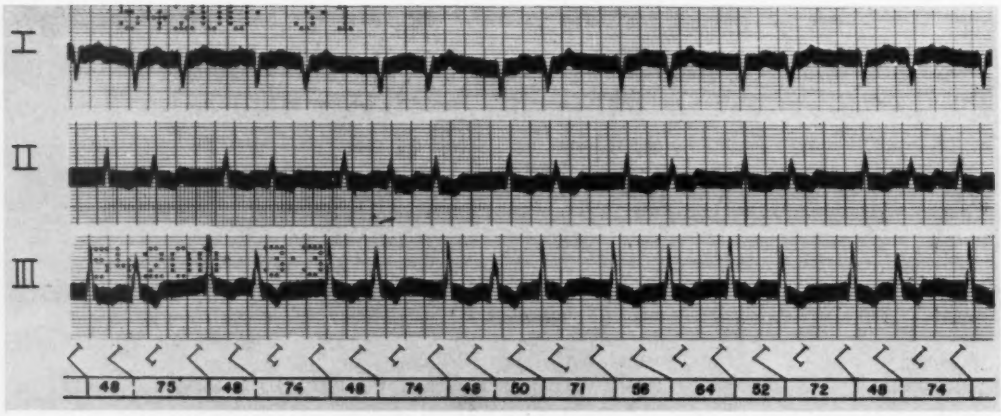

Figure 2

Nonparoxysmal A-V nodal tachycardia with 3:2 or 4:3 forward block and aberrant ventricular conduction imitating bigeminy due to ventricular ectopic beats. Atrial fibrillation and complete A-V dissociation.

the following beat shows aberrant ventricular conduction.[5] Thus, during bigeminy (3:2 ventricular response), every other ventricular complex reveals aberration (cf. second, fourth, sixth, and fifteenth beat of lead III), whereas during trigeminy (4:3 ventricular response) only the second beat of the group is aberrant (cf. eighth beat of lead III). However, with larger increments in the conduction time from the nodal pacemaker to the ventricles (cf. eleventh and thirteenth beat of lead III) the ensuing ventricular cycle becomes long enough to provide sufficient recovery from the preceding stimulation, so that aberration of intraventricular conduction no longer occurs. The absence of aberrant ventricular conduction in the ninth beat of lead III depends not only on the slightly longer cycle (0.50 second) preceding it, but also on the fact that the cycle before that is short.[5]

II. A-V Nodal Tachycardia with Block in the Presence of Sinus Rhythm and Incomplete A-V Dissociation

Figure 3 shows portions of a long record in a 5-year-old boy without clinical evidence of heart disease other than attacks of rapid irregular rhythm before treatment. In both leads, large upright P waves are discernible at an uneven rate of 79 to 91. The ventricular action is much faster (average 125) and more irregular in that short cycles alternate with longer ones (bigeminy). The "coupling" of the early beat is constant (0.34 second), its QRS is prolonged to 0.12 second with features of right bundle-branch block (clearly evident in precordial leads not shown), but there is considerable variability in the size and direction of the main QRS deflections. Contrariwise, the longer cycles vary in duration from 0.50 to 0.66 second but are terminated by beats with less QRS prolongation and with minor variations in contour. The "coupled" beats (R-R 0.34 second) and those with the longest R-R (0.66 second) either coincide with P waves or a P wave precedes or follows them at a short distance. All other beats, with R-R in the intermediate range, are linked to P waves at a P-R interval that varies inversely with the respective R-P distances.

These data lend themselves to two possible alternative interpretations indicated in the two diagrams under lead III. In both, incomplete A-V dissociation is evident—caused by enhancement of impulse formation in the A-V node —with unidirectional retrograde block and aberrant ventricular conduction in the beats terminating short ventricular cycles. In the longer diagram on the left, the bigeminy is attributed to the operation of two nodal centers: a higher one escaping at an accelerated rate of approximately 91 (ventricular cycle length 0.66 second) and a lower one coupled to each upper nodal beat as well as to each ventricular capture by a sinus impulse. Partial (concealed) retrograde conduction of lower nodal impulses seems to prevent the continuity of regular discharges of the upper nodal center.[6] This latter interpretation, however, appears less likely than the one indicated in the diagram on the right and shown throughout the diagram under lead aV_F. Here the A-V dissociation is ascribed to the action of a single nodal pacemaker, faster than the sinus, releasing impulses in regular sequence and

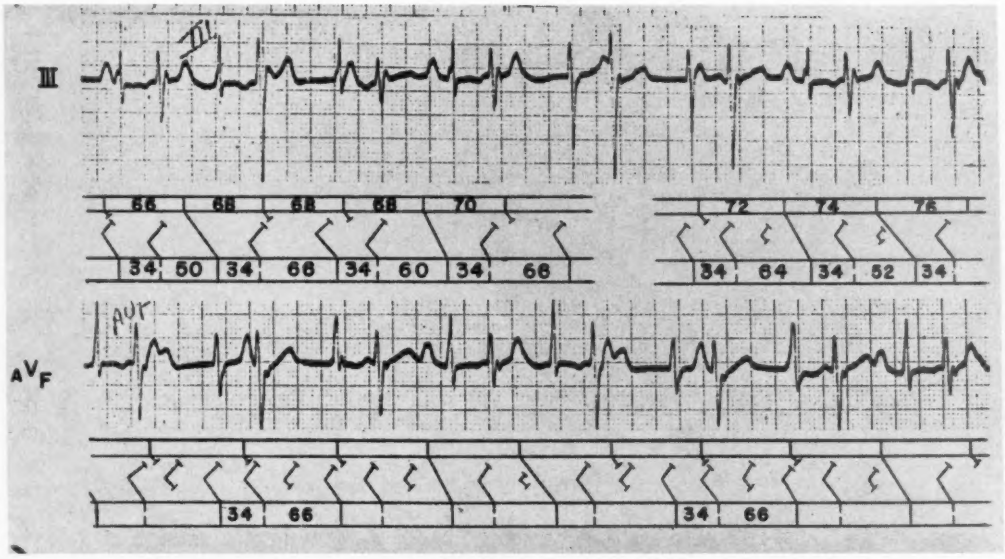

Figure 3

A-V nodal tachycardia with 3:2 forward block and aberrant ventricular conduction during sinus rhythm resulting in incomplete A-V dissociation and persistent ventricular bigeminy. (Courtesy of Dr. Leonard S. Dreifus, Hahnemann Medical College, Philadelphia).

having a 3:2 forward block. When a sinus impulse occurs at an opportune time during the intermittence, it is conducted to the ventricles (capture), shortens the pause, and postpones the next nodal discharge. The rate of this single nodal pacemaker can be determined in lead aV_F by dividing the distance that separates the first nodal beats following an intermittence by three $\frac{(0.34 + 0.66}{3} =$ 33.3 second). This corresponds to a rate of 180, which is within the usual range of paroxysmal types of nodal tachycardia.[3] Thus, while there is a complete block of retrograde conduction in the upper A-V junction, forward conduction through the lower junction takes place at a persistent 3:2 ratio with a Wenckebach phenomenon. This mode of conduction is maintained when a ventricular capture by a sinus impulse replaces the first nodal beat after the intermittence. The result is continuous ventricular (pseudo-) bigeminy.

Table 2

Structure of an Arrhythmia Caused by a Conduction Disturbance of the Wenckebach Type

1. Groups of short cycles are separated by pauses.
2. Progressive shortening of successive short cycles.
3. Pauses are shorter than the sum of two successive short cycles.
4. First cycle after a pause is longer than the last cycle before the pause.

III. A-V Nodal Tachycardia with Forward Block in the Presence of Retrograde Conduction

Figure 4 is a long continuous record of lead II obtained in a 53-year-old man with rheumatic heart disease. In the first part of the upper strip, the P waves are inverted and occur at an almost regular rate (125 to 130 per minute), precisely twice as fast as that of the ventricles. This sequence is disturbed toward the end of the strip, at first by a short ventricular cycle of 0.58 second (exceeding the corresponding P-P interval by 0.08 second) and then by a premature P wave that is somewhat more inverted than the preceding ones. This, in turn, is followed, after standstill of atria and ventricles for 1.98 and 2.72 seconds, respectively, by three upright P waves, all of which are linked to QRS complexes at a P-R of 0.28 second. (The first P-P and R-R intervals are longer than the second ones). Subsequently, another regular series of fast inverted P waves (P-P, 0.48 second) sets in and continues to the end of the record. At this time, however, the ventricular action is irregular—at first fast, with progressively shortening R-R intervals (from

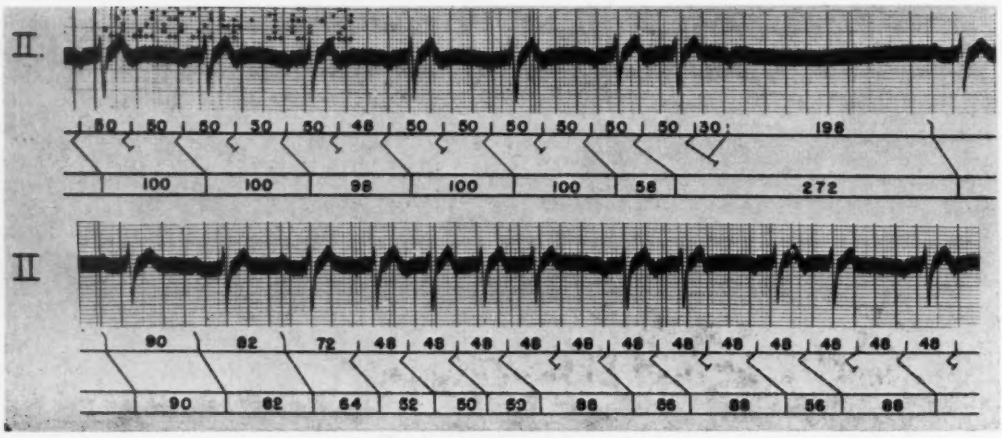

Figure 4

A-V nodal tachycardia with retrograde conduction and second-degree A-V block of forward conduction interrupted by atrial re-entry. Continuous long lead II; the last P-QRST combination of the upper strip is reproduced as the first in the lower strip.

0.64 to 0.50 second), and then slower, with R-R intervals alternating between 0.88 and 0.56 second (bigeminy).

These apparently complex conditions lend themselves to the uniform interpretation indicated in the diagram. At the beginning and end of the tracing, a regular A-V nodal tachycardia is present. All retrograde impulses reach the atria at a constant conduction velocity whereas forward conduction to the ventricles is either delayed or blocked in the lower part of the A-V junction. A series of 2:1 ventricular responses (at the beginning of the record) results in a slow and regular ventricular rate, a series of 3:2 responses (at the end of the record) leads to ventricular bigeminy, and a series of four impulses conducted with the Wenckebach phenomenon in the (middle of the lower strip) causes a characteristic ventricular arrhythmia (table 2). On one occasion (toward the end of the upper strip), however, the regular nodal activity is disturbed by an impulse arising earlier; this impulse is propagated backwards into the atria but not to the ventricles. The origin of this premature impulse could be a sporadic discharge of another nodal center but the explanation presented in the diagram appears more likely. This diagram represents re-entry into the atria of the preceding nodal forward impulse that penetrated slowly into the A-V junction but failed to reach the ventricles.[7, obs., 94] On its way to the atria the re-entrant impulse had to pass the point of its origin, which it discharged prematurely and, in addition, it transiently depressed the activity of this pacemaker.[8] Thus, for about 2 seconds, atria and ventricles remain without stimulation. During the pause, impulse formation in the sinus pacemaker, subdued during the preceding ectopic activity, is gradually re-established and the sinus node takes over control of the heart for three beats, to be replaced by the A-V node when the more rapid impulse formation in the original ectopic A-V nodal center resumes its activity.

Figure 5 is a tracing obtained in a 4-year-old boy, 5 hours following repair of a ventricular septal defect by open-heart surgery. There is repetitive grouping of atrial and ventricular complexes. The former, represented by retrograde P waves, occur in groups of three; the latter, represented by normal QRS complexes (with S-T slightly depressed), are arranged in groups of four. In both, there is progressive reduction in the duration of successive short (P-P or R-R) intervals, and the pauses separating the faster atrial beats are shorter than the sum of any three short ones, while those separating the faster ventricular beats are shorter than two successive short ventricular cycles. This again is the typical structure of a Wenckebach period (table 2), which in this instance seems to involve both forward and retrograde conduction of impulses regularly originating in the A-V junction.

Two possible alternative interpretations are indicated in the diagrams. At the left, a regular *continuous* nodal tachycardia (rate 167) is assumed with a 5:4 response of the ventricles and a 5:3 response of the atria. Failure of two

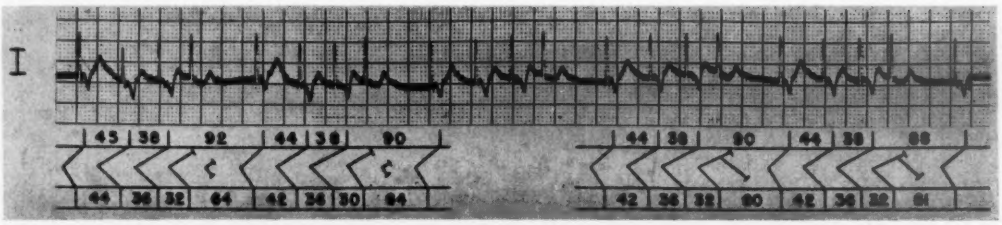

Figure 5

Nonparoxysmal A-V nodal tachycardia with Wenckebach periods of forward and retrograde conduction. (Courtesy of Dr. E. O. Theilen, State University of Iowa, Iowa City).

successive retrograde impulses to reach the atria is attributed to concealed retrograde conduction of the fourth impulse in each group. Thus, the manifest 5:3 response of the atria is actually an unsuccessful attempt at a 5:4 response, corresponding to that actually occurring in the ventricles. In the diagram at the right, the longer ventricular cycles are attributed to incomplete (concealed) re-entry[9, 10] of the nodal impulse with maximal retardation of retrograde conduction, i.e., the blocked impulses. Only the blocked retrograde impulse periodically interrupts the continuity of the nodal tachycardia because the degree of its retardation of conduction is sufficient to permit re-entry. Both interpretations are in keeping with present knowledge concerning the physiology of atrioventricular junctional tissues.[11, 12]

IV. Double A-V Nodal Tachycardia with A-V Dissociation

The two records in *figure 6* are from different patients with arteriosclerotic heart disease—record A, is from a 70-year-old woman, and record B, is from an 80-year-old man. They have in common (a) regular retrograde P waves recurring at a rate which is slower than that of the ventricles, and (b) ventricular complexes with normal QRS duration, the ST-T of which is deformed by a digitalis effect. They differ in that the ventricular action is regular throughout in record A, whereas in B, this regularity is disturbed by an occasional earlier beat occurring at a predictable time, i.e., whenever a (retrograde) P wave follows a QRS at a sufficiently long, but not too long, R-P interval. Obviously, in both records there is A-V dissociation, complete in record A and incomplete (with ventricular captures) in record B. It is engendered by the simultaneous operation of two supraventricular ectopic pacemakers. One activates the atria in retrograde fashion, the other is in permanent or almost permanent control of the ventricles.

As indicated in the diagrams, both of these pacemakers can be assumed to be located in the A-V junction, though at different levels. In A, mutual complete "protection" of one pacemaker from the impulses of the other, and undisturbed regular activity of each, seems to be maintained by a physiologic state of refractoriness in the intermediate path between them, which is entered in rapid succession by oppositely directed impulses. In B, where the rate of the two pacemakers is slower, some depression of A-V conductivity must be present to account for the permanent failure of the lower retrograde nodal impulses to reach higher junctional levels (and to disturb the regularity of the slower upper pacemaker). However, this impairment of impulse propagation can only be unidirectional, since appropriately timed antegrade impulses of the upper pacemaker succeed in traversing the A-V junction and in capturing the ventricles. A transient prolongation of the R-R interval following the ventricular capture indicates some depression of the lower (faster) nodal pacemaker due to its premature forced discharge by the passing impulse of the higher (slower) pacemaker.[8]

V. A-V Nodal Tachycardia with Aberrant Ventricular Conduction in Alternate Beats Resulting in a Bidirectional Type of Tachycardia

The tracing in *figure 7* was obtained in a 67-year-old man with arteriosclerotic heart disease who died on the day of admission. The ventricular rate is rapid (176 per minute) and precisely regular; QRS is of normal duration in all leads shown, but no P waves are discernible. A fast ectopic pacemaker controls the ventricles, either in the presence of atrial fibrillation and complete A-V dissociation or with simultaneous retrograde activation of the atria. In leads II and III, all ventricular complexes have the same contour, the ST-T being deformed by typical digitalis effects. In the A-V limb leads, however, there is an alternation in the ventricular complexes involving the direction of QRS. This gives the record a "bidirectional" appearance. Since rate and regularity of the ventricular rhythm did not

Table 3

The Sequence of Therapeutic and Excessive Digitalis Effects in Atrial Fibrillation

Mechanism	Ventricular action
Depression of A-V conduction	Slow and irregular
↓	
A-V nodal escape	Slow and regular
↓	
Acceleration of A-V nodal pacemaker	Faster and regular
↙ ↘	
(a) Block between nodal pacemaker and ventricles	(a) Slower and irregular (Pseudobigeminy)
(b) Further acceleration of nodal pacemaker and alternating aberrant ventricular conduction	(b) "Bidirectional" regular tachycardia

change, and the QRS duration remained normal in all beats, development of a second ectopic (ventricular) pacemaker[13] can be ruled out. It appears rather that, as a consequence of ventricular responses to every impulse of a single rapid A-V nodal pacemaker, a functional conduction disorder developed in the ventricles, affecting the mode of propagation of alternate impulses.[10,14] This then may be considered an unusual variety of electrical alternans due to aberrant ventricular conduction, with the pattern of a bidirectional tachycardia.

Discussion

The five types of A-V nodal arrhythmias illustrated and analyzed in this report have some implications with regard to (1) present knowledge of pathophysiology of the A-V junctional tissues, (2) precision of electrocardiographic interpretation, and (3) the clinical significance of such tracings, especially in relation to digitalis therapy.

The pathophysiology of the A-V junction has become the subject of renewed interest with the introduction of new refined methods for direct recording of bioelectrical manifestations of specific myocardial fibers.[1, 15-19] Experimental study became possible in regard to causes and places of normal and abnormal delays of impulse propagation through the several anatomic subdivisions of the A-V junction. On this basis some concepts, which have been utilized by investigators who are mainly oriented clinically, have gained firm experimental documentation[20-23] and can now be safely applied in resolving some unexpected features of disturbed A-V conduction. For example, the concept of concealed A-V conduction, just recently labeled as "highly theoretical,"[24] can now be based on direct experimental evidence. The other facet of pathologic A-V nodal function, however, disturbance of impulse formation, especially nonparoxysmal tachycardia, has to our knowledge, not yet been approached experimentally. It is hoped that by calling attention to the frequency of this disorder in clinical electrocardiography we will stimulate the experimental cardiac electrophysiologist to reproduce A-V nodal tachycardia in the laboratory animal in order to determine which factors can precipitate, modify, or terminate such a condition.

A-V nodal tachycardia with block has only rarely been recognized as such in the past,[2, 4, 7, 10, 25-30] and the presence of bidirectional conduction block such as illustrated in figure 5, has been erroneously attributed to grossly irregular discharge of the A-V nodal pacemaker.[31] Although, in such cases, direct measurements of A-V conduction times are not feasible, the characteristic structure of the ventricular and atrial arrhythmias (table 2) provides the key to the recognition of second-

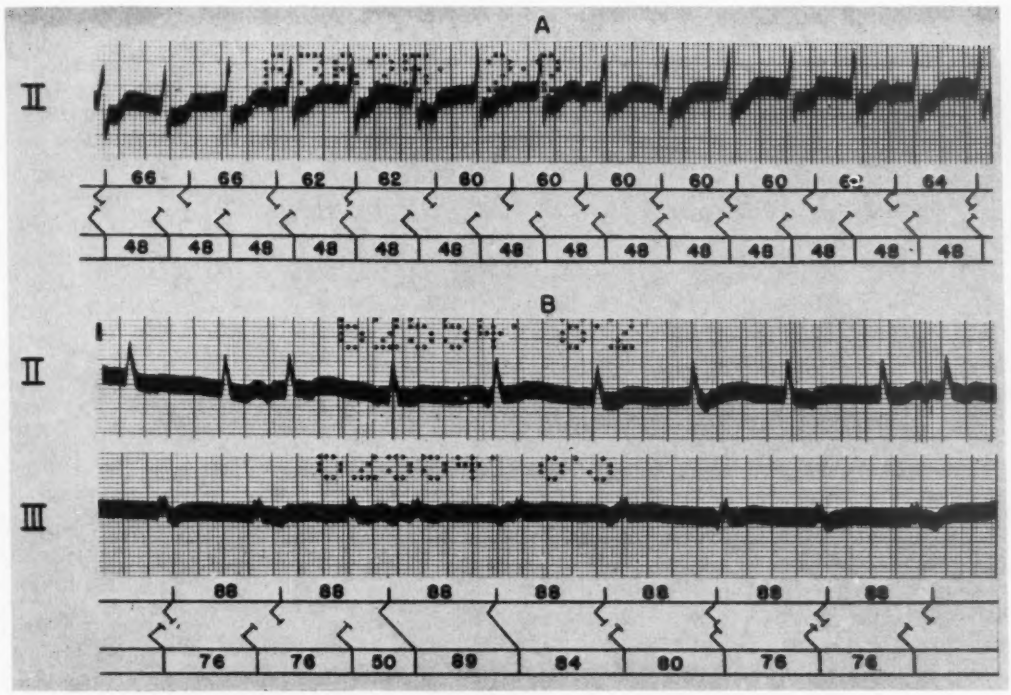

Figure 6

Complete (A) and incomplete (B) A-V dissociation caused by simultaneous operation of two accelerated A-V nodal pacemakers.

degree A-V block with Wenckebach periods.[4, 5] Particularly, the occurrence of A-V nodal tachycardias with block in association with atrial fibrillation has not been sufficiently emphasized. In fact, instances of atrial fibrillation were excluded in some previous studies on supraventricular tachycardias.[32] In such a combination, the true mechanisms can easily be overlooked and the irregular ventricular beating erroneously considered as the usual response to the fibrillatory atrial impulses, unless the rapid and irregular ventricular rate shows the characteristic arrangement of Wenckebach periods and is preceded or followed by a series of rapid regular beats identified as a nodal tachycardia in the presence of complete A-V dissociation (fig. 1). If concealed conduction or conduction during a supernormal phase complicates the transmission pattern of the nodal impulses or of some impulses of the fibrillating atria, then the structure of the ventricular arrhythmia may become atypical and the diagnosis may become impossible. Such nodal tachycardias with totally irregular ventricular responses may conceivably provide the explanation for some instances of "paradoxical" acceleration of the ventricular rate in digitalized cases with atrial fibrillation.[33, 34] Furthermore, a rapid nodal tachycardia with a persistent 3:2 ventricular response and aberrant ventricular conduction[10] may become difficult or impossible to distinguish from bigeminy due to premature ventricular ectopic beats—unless the conduction ratio or conduction time of successive impulses varies and ventricular aberration transiently disappears (fig. 2). The true nature of the arrhythmia may also go unrecognized when 2:1 exit block of rapid nodal impulses, as seen temporarily in figure 2, becomes permanent. Finally, in all such cases the presence of atrial flutter with vary-

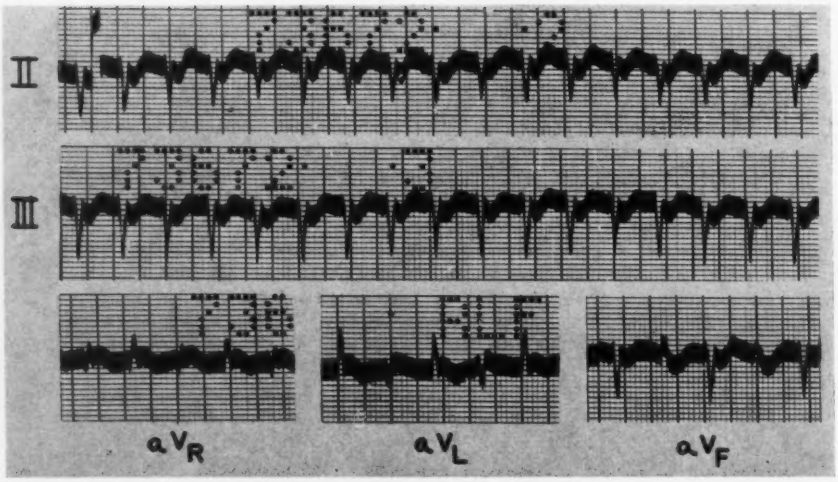

Figure 7

Nonparoxysmal A-V nodal tachycardia with alternating aberrant ventricular conduction causing a "bidirectional tachycardia."

ing ventricular response[5, 35] should be ruled out.

In a previous study,[3] three principal pathogenic factors could be established to be responsible for nonparoxysmal types of A-V nodal tachycardia with or without A-V block, namely acute rheumatic fever, recent posterior wall infarction, and excessive digitalis medication. To these, in our latest experience, a fourth condition was added, namely, early postoperative states of open-heart surgery upon or near the ventricular septum—an example being illustrated in figure 5. It would appear that, like their medical counterpart, surgically induced A-V nodal tachycardias are transitory disorders.[36, 37] Their prognostic significance remains to be evaluated further.

Digitalis induced A-V nodal tachycardias, with or—more frequently—without block in the presence of atrial fibrillation are, in our experience and that of others[30] a more common manifestation of digitalis excess[38] than the so-called PAT with block as described by Lown and Levine.[39] These authors,[40, 41] as well as others,[42, 43] also observed increase and regularization of the ventricular rate of digitalized patients with atrial fibrillation, but they apparently failed to recognize the persistence of a nodal tachycardia with A-V dissociation when the ventricular action became irregular due to the development of a conduction disorder below the nodal pacemaker (table 3). Digitalis-engendered nodal tachycardia, like PAT with block, recently has been reported to respond promptly to potassium infusion in the absence of overt hypokalemia.[37]

Nonparoxysmal nodal tachycardia with and without block is primarily an electrocardiographic diagnosis. In the presence of atrial fibrillation, however, its development can be suspected at the bedside when the following sequential changes in the ventricular action are noted on continued digitalis medication (table 3):

A slow and irregular ventricular rate, caused by depression of A-V conduction, at first becomes regular due to repetitive escape of a slow nodal pacemaker leading to intermittent and later persistent A-V dissociation. With further digitalization this pacemaker, and consequently the ventricular rate, becomes faster but remains regular.[3] After this two events may take place: 1. A block may develop below the ectopic pacemaker to render the ventricular action once again slower and irregular (fig. 1). A persistent 3:2 conduc-

tion ratio of the nodal impulses may result in ventricular bigeminy and be mistaken for bigeminy due to ectopic beats of ventricular origin (fig. 2). 2. There may be further acceleration of nodal activity associated with aberrant ventricular conduction and result in a so-called bidirectional tachycardia,[10] a dangerous manifestation of advanced digitalis toxicity (fig. 7). In the absence of atrial fibrillation, on the other hand, failure to discontinue digitalis in time may lead to acceleration of an additional atrial[2, 28, 44] or nodal[45–47] pacemaker resulting in a double ectopic tachycardia (fig. 6).

Conclusions and Summary

Paroxysmal as well as nonparoxysmal varieties of rapid ectopic rhythms originating in the A-V node may be associated with various conduction disorders involving propagation of regularly generated impulses to the atria and ventricles as well as within the ventricles. This may occur following treatment of a paroxysmal tachycardia by digitalis or when impulse formation within the node becomes accelerated as a consequence of digitalis excess.

Since retrograde and forward conduction may vary independently and since the tachycardia frequently develops in a presence of atrial fibrillation, actual conduction times through the A-V junction may not be measurable. The nature of the arrhythmia must be diagnosed from the spacing and characteristic grouping of ventricular or atrial complexes or from changes in the configuration of the ventricular beats.

Several varieties of such nodal tachycardias with block are presented, including examples of (a) A-V dissociation in atrial fibrillation with Wenckebach periods of forward conduction; (b) A-V dissociation during sinus rhythm with Wenckebach periods of antegrade nodal impulses; (c) Wenckebach periods of forward conduction with constant retrograde conduction; (d) Wenckebach periods of both forward and retrograde conduction, with blocked re-entry as a possible mechanism of intermittence of the tachycardia; (e) complete and incomplete A-V dissociation due to acceleration of two nodal pacemakers; and (f) aberrant ventricular conduction simulating ventricular premature beats or resulting in a bidirectional type of tachycardia.

Acknowledgment

We are indebted to Drs. L. S. Dreifus, of Philadelphia, and E. O. Theilen, of Iowa City, for their courtesy in permitting us to use their observations on figures 3 and 5, respectively.

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Arteriosclerotic Popliteal Aneurysms

Diagnosis and Management

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IN THE FIELD of medicine there are few conditions presenting a threat to life and limb that are as readily diagnosable before the occurrence of catastrophe as aneurysms of the popliteal artery. Moreover, this is a pathologic condition that has been amenable to surgical attack for 200 years, since John Hunter performed femoral artery ligation in the adductor canal. In spite of the potential ease of diagnosis and the availability of successful therapy, most popliteal aneurysms are allowed to go on to disastrous complications, either unrecognized or untreated.

The high incidence of complications has been shown by Gifford, Hines, and Janes[1] in an analysis of 100 cases of popliteal aneurysms. They described acute thromboses in 20 cases, rupture of the aneurysm in 16, peripheral emboli from the aneurysm in 14, and gangrene of the extremity in 24 cases. In addition they reported a limb loss of 23 per cent following conservative treatment, as compared to 8 per cent following surgical intervention. Linton[2] reported an amputation rate of 77 per cent in untreated cases. In his series of operative cases, sympathectomy followed by aneurysmectomy, there were no amputations. Other reports[3-8] have indicated equally good results following surgical intervention. Lord[9] advocated endoaneurysmorrhaphy in patients who are poor surgical risks or who have no distal pulses. In good-risk patients and in those with pedal pulses he employed venous autografts. Austin and Thompson[3] and Bahnson[4] have had success with homografts, and Julian et al.[6] reported the restoration or preservation of ankle pulses in seven of nine cases with the use of venous autografts or homografts.

These series indicate the generally successful results that can be obtained by the surgical approach, varied though it may be. The important feature is the early diagnosis and the recognition of the potential seriousness of the untreated condition.

The purpose of this paper is to elucidate the clinical features of arteriosclerotic popliteal aneurysms and to illustrate the various surgical methods of treatment that are available and may be particularly suited to the individual case.

Table 1 summarizes the major features of each patient. Certain of these cases are reported in detail below, followed by comments regarding the salient points of diagnosis and treatment.

Case Reports

Case 1

A 32-year-old white man, previously well, appeared with a 1-week history of pain and swelling behind the right knee. Examination revealed a pulsatile mass in the right popliteal area associated with a bruit. Posterior tibial and dorsalis pedis pulses were present. The serologic test for syphilis was negative. An arteriosclerotic aneurysm of the popliteal artery was resected with restoration of arterial continuity by means of an iliac artery homograft inserted end-to-end. Good pedal pulses were noted postoperatively. Nine months later the pedal pulses had disappeared and the oscillometric readings below the knee were greatly reduced. It is likely that occlusion of the homograft has taken place. His only symptom, however, is mild claudication after walking three or four blocks.

Although the majority of arteriosclerotic aneurysms, popliteal and otherwise, are found in the older age groups, one must still consider their possibility in younger individuals. A pulsatile mass and a bruit are diagnostic at any age. An effort should be made to establish arterial continuity after resection of the aneurysm, if the popliteal branches are patent. This case is also an example of homograft failure, of which many others have been reported in the recent literature. It is probable that the occlusion of the homograft was gradual, allowing sufficient collateral circu-

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Table 1

Summary of Cases of Popliteal Aneurysms

Case no.	Age	Sex	Symptoms	Findings	Pulses Pre-op.	Surgery	Results
1	32	M	Painful swelling	Arteriosclerotic aneursym; no thrombosis or leakage	Present	Resection and iliac artery homograft	Pulses maintained; good initial result; absent pulses 9 months later
2	62	M	Calf pain, blotching, and coldness	Compression of popliteal veins by aneurysm producing phlebitis	Present	Sympathectomy followed by resection and venous autograft	Excellent pulses present 4 years later
3	56	M	Pain followed by claudication and numbness	Dissecting aneurysm with recent thrombosis	Absent	Resection and Teflon prosthesis	Excellent restoration of pulses; claudication gone
4	73 Rt.	M	Sudden pain and discoloration 4 days	Thrombosed popliteal aneurysm, rapid gangrene	Absent	Thigh amputation	Working with prosthesis 3½ years
	Lt.		Asymptomatic mass in popliteal area	Probable old thrombosed aneurysm; history suggesting arterial insufficiency in the past	Absent	None	
5	65 Lt.	M	Pain, coldness and discoloration following recent trauma	Thrombosed popliteal aneurysm	Absent	Exploration popliteal artery; thrombosis involved branches of artery; could not restore circulation	Below-knee amputation
	Rt.		Asymptomatic	Arteriosclerotic aneurysm without thrombosis or leakage; major branches aneurysmal	Present	Sympathectomy followed by ligation of popliteal artery	Good results; no symptoms
6	75	M	Pain and enlarging mass	Aneurysm with evidence of old and recent leakage	Absent	Ligation in adductor canal	Can walk 8 to 10 blocks without pain
7	62	M	Pain and coldness	Multiple aneurysms of femoral and popliteal arteries with recent thrombosis; amputation of opposite leg 4 years previously	Absent	Exploration of artery; circulation could not be restored; lumbar sympathectomy	Amputation below knee
8	50 Lt.	M	Pain, coldness, and numbness	Recent thrombosis involving popliteal aneurysms and extending proximally into femoral artery and distally into all branches	Absent	Exploration of artery; unable to restore circulation; lumbar sympathectomy	Above-knee amputation
	Rt.		Asymptomatic	Pulsating aneurysm	Present	Awaiting excision and graft	
9	44	M	Pain and tightness in popliteal space; recent injury to knee	Pulsating aneurysm involving popliteal artery and all three branches	Present	Lumbar sympathectomy followed by excision of aneurysm 2 weeks later; no graft	Good result; no claudication; 4 years later pedal pulses noted due to excellent collateral circulation

lation to develop so that the ensuing symptoms were minimal.

Case 2

A 62-year-old white man developed pain in the left calf, becoming progressively worse and associated with cyanotic blotching or mottling of the skin and coldness of the foot. There was no history of trauma. Examination revealed tenderness of the left calf, cyanosis of the skin, and a positive Homans' sign. A pulsating aneurysm of the left popliteal space was also felt; the pedal pulses were present. A diagnosis of deep thrombophlebitis was made, and it was thought that this condition was secondary to compression of the popliteal vein by the aneurysm.

The patient was treated with anticoagulant drugs and showed improvement in his symptoms and disappearance of the discoloration. A left lumbar sympathectomy was then performed. Two weeks later the popliteal aneurysm was excised and arterial continuity was re-established with a venous autograft taken from the ipsolateral great saphenous vein. His postoperative course was uneventful, and 4 years later excellent pedal pulses were noted in the operated leg. He had no residual symptoms except for minimal swelling, which was probably secondary to his previous phlebitis and varicosities.

Compression of the popliteal vein is one of the complications of popliteal aneurysm. In view of the close proximity of the artery and vein in the relatively closed space, one wonders why this complication is not more often noted. The increasing obstruction to the popliteal vein may result first in edema and eventually in thrombosis, as illustrated in this case. The enlarging aneurysm may also press on the tibial and peroneal nerves causing considerable pain in the areas of their distribution. The end result with the venous autograft in this case is consistent with that reported in Lord's series.

Case 3

A 56-year-old white man noted the sudden onset of cramping pain in the right calf followed by numbness in the foot. Popliteal and pedal pulses were absent on the right and normal on the left. A popliteal mass was not discernible. A percutaneous femoral arteriogram disclosed occlusion of the popliteal artery, but the diagnosis of aneurysm was not established. Operation revealed a long, fusiform aneurysm of the popliteal artery, which was resected, and the blood flow was re-established with a 3/8-inch woven Teflon prosthesis. The specimen measured 6.2 cm. in length and 0.8 to 1.0 cm. in diameter. When the aneurysm was opened, it was found to be a dissecting aneurysm, the dissection occurring between the inner two thirds and outer one third of the media. There was fresh thrombus in the false lumen, compressing but not completely occluding the true lumen. Postoperatively the patient did well with complete relief of his symptoms and restoration of both pedal pulses.

Although one usually associates arterial dissection with the aorta, especially the arch and thoracic portions, it can occur in other vessels that are arteriosclerotic, and should be considered in the differential diagnosis of acute arterial occlusions.

Case 4

A 73-year-old man was admitted with a history of sudden pain and discoloration of the right leg 4 days in duration. Examination revealed a cold, pulseless, mottled lower leg. Gangrene and toxicity rapidly developed, necessitating a low-thigh amputation. Examination of the specimen showed a typical arteriosclerotic aneurysm well localized to the popliteal artery and containing old and fresh thrombus. Postoperatively he did well and has been fitted with a prosthesis. He has been completely rehabilitated. Examination of the opposite leg in this patient revealed a thrombosed aneurysm of the popliteal artery with pulsation in the femoral artery down to the aneurysm but no pulsations distally. He had minimal symptoms of arterial insufficiency in this leg and described an episode suggestive of acute occlusion in the past.

The development of an arteriosclerotic popliteal aneurysm ordinarily does not in itself produce significant collateral circulation in the extremity, such as is usually noted in gradually obliterative arteriosclerosis. When acute occlusion due to thrombosis does occur, collateral circulation is inadequate, and the outcome is usually gangrene.

Case 5

A 65-year-old white man was admitted to the hospital with pain, coldness, and discoloration of the left leg following trauma. Examination disclosed evidence of a thrombosed popliteal aneurysm with no distal pulses. At operation the thrombotic process extended into the major branches of the popliteal artery. It was impossible to remove the thrombus completely. Gangrene developed, necessitating amputation below the knee.

The diagnosis of a popliteal aneurysm of the opposite leg was made during the same admission. This aneurysm was pulsatile and pedal pulses were present. A right lumbar sympathectomy was performed followed by exploration of the popliteal artery 1 week later. A large, pulsating aneurysm was present, involving the popliteal trifurcation so that grafting was not feasible. The arterial branches were ligated close to the aneurysm, and the popliteal artery was divided im-

mediately proximal to the aneurysm without disturbing collateral circulation. Postoperatively he did well and had no symptoms in that leg.

Case 6

A 75-year-old man complained of progressive pain in the left thigh and popliteal area associated with an enlarging mass in this region. Examination revealed a large pulsatile mass in the popliteal area with considerable tenderness, induration of the overlying tissues, and ecchymotic discoloration. There were no distal pulses. On exploration a large arteriosclerotic aneurysm of the popliteal artery was found. This was surrounded by marked inflammatory reaction, almost of a granulomatous type, the result of previous episodes of leakage from the aneurysm. There was also evidence of recent leakage but no massive hemorrhage. Smaller aneurysms were present along the course of the femoral artery associated with considerable atherosclerotic changes.

Owing to the marked inflammatory reaction surrounding the aneurysm, the involvement of the major branches of the popliteal artery, the extensive atherosclerotic changes, and the patient's poor general condition, it was not considered advisable to resect the aneurysm or to try to maintain arterial patency. The superficial femoral artery was ligated in Hunter's canal as close as possible to the aneurysm to preserve proximal collateral vessels. This procedure was very similar to that described by John Hunter in the eighteenth century. Postoperatively the foot remained warm and of good color, with no evidence of ischemia. The postoperative course was complicated by deep thrombophlebitis that was treated with anticoagulant drugs. Ten months later the patient was able to walk 8 to 10 blocks without stopping with no symptoms referable to the operated leg other than residual edema well controlled with an elastic stocking.

Rupture of a popliteal aneurysm is not an uncommon complication. If untreated, death may result from continued loss of blood and toxic absorption. If grafting is not feasible, then obliterative endoaneurysmorrhaphy or a simple ligation of the popliteal artery above the aneurysm will suffice to prevent further leakage or frank hemorrhage.

Case 7

A 62-year-old white man developed sudden pain and coldness of his left leg. He was mildly diabetic, and 4 years previously had had mid-thigh amputation of the right leg for arteriosclerotic gangrene. The left leg was noted to be cold and mottled below the knee. Popliteal and pedal pulses could not be felt but at surgery small pulsatile aneurysms were found along the entire course of the femoral artery. Calcification in these aneurysms was readily demonstrated by x-ray.

A left lumbar sympathectomy was performed followed by immediate exploration of the popliteal artery. This was found to be aneurysmal also and completely occluded by a thrombus that extended into all the distal branches. A thrombectomy was performed but retrograde blood flow could not be obtained. He subsequently developed gangrene of the lower third of the left leg. After a below-knee amputation this patient had an uneventful recovery. He is ambulatory with bilateral prostheses.

Case 8

A 50-year-old white man was seen approximately 8 hours following the sudden onset of pain, coldness, and numbness of the left leg. The leg was cold and pale from the mid-thigh downward, with no pulses below the femoral artery in the groin. He could not move his toes or foot.

A lumbar sympathectomy was performed immediately, followed by exploration of the femoral-popliteal artery. This revealed extensive atherosclerosis of the femoral artery with a popliteal aneurysm. Both the artery and aneurysm were completely occluded by a recent thrombus that involved all the major branches and collateral blood vessels. Blood flow could not be re-established. He rapidly developed gangrene. This necessitated an above-knee amputation, which healed satisfactorily.

Examination of the opposite leg revealed a pulsating popliteal aneurysm with pedal pulses. He is now awaiting operation on the right leg.

Case 9

A 44-year-old man noted pain and tightness in the right popliteal area shortly following an injury to that region. Examination revealed a pulsatile aneurysm of the right popliteal artery with good pedal pulses. A lumbar sympathectomy was performed, followed by exploration of the aneurysm in 2 weeks. The aneurysm was found to involve the entire popliteal artery and the trifurcation, so that the insertion of a graft was not feasible. The aneurysm was excised without an attempt to restore arterial continuity. Immediately following operation there were no pulses in the foot, but it was warm, of good color, and showed no arterial insufficiency. When last seen, 4 years later, he had excellent pedal pulses on the right leg and the oscillometric readings at the right ankle were almost as good as those on the left. He had no claudication.

The reappearance of the pedal pulses was due to the combined effects of the lumbar sympathectomy and the preservation of all collateral circulation during the excision of the aneurysm.

Results

Nine patients with a total of 12 popliteal aneurysms are reported.

Three extremities were treated with resection of the aneurysm and restoration of blood flow by a homograft, venous autograft, or plastic prosthesis. The initial results in all three cases were good, with maintenance or restoration of the pedal pulses in each case. Good results were maintained in two of the extremities to the present time. In one case pulses disappeared 9 months after operation owing to failure of the homograft.

Three extremities were treated by ligation of the popliteal artery or excision of the aneurysm with or without lumbar sympathectomy. In all three cases viability of the extremity was assured, and the patients were asymptomatic at follow-up.

In four extremities acute thrombosis of the aneurysm was the presenting feature and gangrene of the extremity resulted in all. Direct surgical attack on the aneurysm to establish pulsatile blood flow in conjunction with lumbar sympathectomy did not assure survival of the limb. These results indicate the serious nature of thrombosis of a popliteal aneurysm in regard to survival of the limb and speak for earlier diagnosis before this complication occurs.

Discussion

The diagnosis of popliteal aneurysm will be missed in most cases unless careful palpation of the popliteal area is part of every physical examination. Except for the occasional occurrence of symptoms due to pressure on the popliteal vein or the adjacent nerves, popliteal aneurysms are generally silent. Symptoms sufficient to call attention to the aneurysm are manifestations of catastrophic complications such as thrombosis or rupture.

Because of the absence of a significant history, it may be difficult to distinguish an aneurysm from a popliteal cyst or tumor. In such cases femoral arteriography by percutaneous injection may be helpful. A popliteal aneurysm will rarely be demonstrated as a saccular structure filled with opaque medium, but rather will give the appearance of an arterial occlusion, even when there is no evidence of diminished blood flow distal to the aneurysm. On the other hand a popliteal cyst or tumor will not disturb the normal arterial contour, unless it is causing so much extrinsic pressure that reflex vasospasm will cause a clinical picture of complete arterial occlusion.

As the reported series has demonstrated, various forms of treatment may be employed. Resection of the diseased artery and restoration of arterial continuity is the procedure of choice. On the basis of our experience with various types of grafts in other areas we believe that a venous autograft is best for popliteal artery replacement, because a relatively short segment of vessel of small lumen is needed. If a venous autograft is not suitable, due to technical reasons, then arterial continuity can be restored with a plastic prosthesis such as Teflon. It is not always feasible, however, to do a grafting operation, especially if the aneurysm extends beyond the popliteal trifurcation or when there are extensive and diffuse degenerative changes of most of the femoral artery. The danger of thrombosis of a very long graft or one of very small caliber is so great that we believe one of the older procedures such as endoaneurysmorrhaphy or Hunterian ligation is less likely to produce dangerous ischemia, especially if reinforced by lumbar sympathectomy. In our experience all the types of operation used gave uniformly satisfactory results in uncomplicated popliteal aneurysms.

On the other hand, once thrombosis occurred, no form of treatment seemed capable of saving the overwhelming majority of the involved limbs. If the patient with the dissecting aneurysm is omitted, since his thrombosis involved only the false lumen, it will be seen that only one patient escaped amputation after his aneurysm thrombosed. Treatment by sympathectomy may lower the level of amputation but restoration of blood flow is generally impossible.

Summary and Conclusion

1. Arteriosclerotic popliteal aneurysms are usually asymptomatic until complications oc-

cur. These complications are nerve pressure, popliteal thrombophlebitis, hemorrhage from the aneurysm, and acute thrombosis of the aneurysm. 2. Diagnosis is relatively easy and can be accomplished usually by simple palpation of the popliteal space. 3. Femoral arteriography differentiates aneurysms from extravascular popliteal masses. 4. Various forms of surgical treatment have been shown to be satisfactory in the uncomplicated cases. 5. Of the complications described, leakage is consistent with salvage of the limb but thrombosis is more frequent and usually necessitates amputation. Early diagnosis and treatment are obviously desirable.

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Leopold Auenbrugger
1722—1809

Many doctors paid absolutely no attention to Auenbrugger's discovery. Others declared that it was not a discovery at all, that there was nothing new in what he wrote, since it was to be found in the Hippocratic writings. Yet others regarded percussion as a needless molestation of the sick. Much more distressing to Auenbrugger was de Haen's cold and stubborn silence, for the Dutchman was antagonistic to innovations, took no notice of them, contemptuously ignored them. Nevertheless if there was any place where the new method might have proved fruitful, it was at the Viennese clinic.

Still the book was widely read, so that in two years a new edition was called for. Many of its readers recognized its importance. Haller declared that percussion was 'worthy of close attention, and, it would seem, an entirely new discovery. It is true that proposals of this kind must not be unhesitatingly accepted, but they deserve our respectful attention.'—Henry E. Sigerist, M.D. *The Great Doctors.* New York, W. W. Norton & Co., Inc., 1933, p. 241.

Serum Sodium and Potassium in Essential Hypertension

By BERNARD E. LEVINE, M.D., JOHN M. WELLER, M.D., AND RICHARD D. REMINGTON, PH.D.

DIFFERENCES have been noted between normotensive and hypertensive individuals in salt intake,[1] intracellular electrolytes,[2] total body electrolytes,[3] serum electrolytes,[4] and the renal excretion of sodium and water.[5] If changes in serum sodium concentration reflected intracelluar or metabolic alterations in electrolyte balance, an easily determined factor would be available for study of electrolyte abnormalities in relation to the development of hypertension. Three investigators have reported a slight increase in serum sodium concentration in patients with essential hypertension,[4, 6, 7] whereas two other studies report no difference.[8, 9] The purpose of this study was to define more accurately the associations between serum sodium, serum potassium, and blood pressure level by standardizing to the greatest degree possible all methods and measurements, and by assessing the importance of such variables as age, sex, and body build. An additional purpose was to evaluate further the relationship of stated salt intake to blood pressure level and serum electrolyte concentrations.

Methods

Selection of Subjects

Male and female normotensive and hypertensive inpatients and outpatients, free from any disease other than essential hypertension that might affect blood pressure or serum sodium level, were selected. Evident renal, cardiac, and adrenal disease, as well as diabetes mellitus, were causes for exclusion. Hypertensive patients with renal, cerebral, or cardiac complications, or who were on antihypertensive medication, were also excluded. Within these limitations unselected normotensive patients and consecutive clinic patients with hypertension were studied. Information was collected on each about age, sex, race, height, weight, personal and family history of hypertension, and previous and present salt intake (by use of questions outlined by Dahl[1]). All inpatient blood pressures were taken upon awakening of the subject in the morning. All outpatient pressure readings were taken after the patients had rested for 15 minutes. In every case the patient was recumbent and the cuff was placed on the right arm. The level when Korotkoff's sounds first appeared was recorded as the systolic pressure and the level of complete disappearance as the diastolic pressure. Hypertension was defined as either a systolic blood pressure reading above 140 or a diastolic reading above 90 mm. Hg. Mean blood pressure was calculated as the diastolic pressure plus one third of the pulse pressure. Venous blood was collected from patients who were fasting or were more than 3 hours postprandial. It was centrifuged within 2 hours of collection and the serum was frozen. To reduce day-to-day variations in methodology, data were recorded and groups of sera from both normotensive and hypertensive patients were analyzed by flame photometry for sodium and potassium during the same period.

Data were obtained on 118 patients (69 normotensive and 49 hypertensive) but were complete for 50 normotensive and 43 hypertensive patients. Patients were between ages 20 and 60. Sixteen of the 118 values of serum sodium were outside the range of 130 to 155 mEq. per liter and six serum potassium levels were outside 3.5 to 5.5 mEq. per liter. These were considered to be evidence of unknown disease or laboratory error and were rejected. The distribution of these discarded values showed no relation to blood pressure.

Statistical Analysis

Statistical analyses were completed to evaluate many relationships as shown in tables 1, 2, and 3. As a preliminary step in the analysis of the difference in serum sodium and potassium levels in the hypertensive versus the normotensive group, a Chi-square test of the difference between the sex composition of the two groups was completed. This shows a significantly higher proportion of women in the hypertensive group than in the normotensive group (Chi-square = 5.13, $0.01 < p < 0.025$). Furthermore, the two groups are of

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Supported in part by a grant from the American Heart Association.

Table 1

Serum Sodium and Hypertension

Group of subject's	Normotensive: Number of patients	Normotensive: Mean serum sodium (mEq./L.)	Hypertensive: Number of patients	Hypertensive: Mean serum sodium (mEq./L.)	t	Degrees of freedom	p
Men under 40 years of age	24	141.9	7	142.0	0.05	29	$p > 0.80$
Men 40 to 49 years of age	9	142.0	8	140.8	−0.53	15	$0.60 < p < 0.80$
Men over 49 years of age	8	145.1	8	139.9	−2.82	14	$0.01 < p < 0.02$
Women under 40 years of age	8	142.2	2	143.2	0.20	8	$p > 0.80$
Women 40 to 49 years of age	8	140.5	13	141.7	0.58	19	$0.40 < p < 0.60$

Table 2

Serum Potassium and Hypertension

Group of subjects	Normotensive: Number of patients	Normotensive: Mean serum potassium (mEq./L.)	Hypertensive: Number of patients	Hypertensive: Mean serum potassium (mEq./L.)	t	Degrees of freedom	p
Men under 40 years of age	25	4.98	7	4.97	−0.07	30	$p > 0.80$
Men 40 to 49 years of age	8	4.93	9	4.96	0.34	15	$0.60 < p < 0.80$
Men over 49 years of age	7	4.95	9	4.84	−0.97	14	$0.20 < p < 0.40$
Women under 40 years of age	7	4.69	1	4.69	0.00	6	$p > 0.80$
Women 40 to 49 years of age	8	4.98	13	4.85	−0.71	19	$0.40 < p < 0.60$

significantly different age, the average age of the normotensive subjects being 38.6 years and that of the hypertensive patients 45.9 years ($t = 4.26$, $p < 0.005$). Since the factors of age and sex are associated in the two groups, the significance of the difference between the average serum sodium and serum potassium was tested, age-sex specified, by the t test. An initial examination of the assumptions of normality of distribution and equality of variance showed that they were sufficiently well satisfied to permit the valid application of the t test.

Results

Serum Electrolytes

There was no significant difference between the mean serum sodium of the hypertensive group and that of the normotensive group (table 1). A similar statement applies to mean serum-potassium (table 2). These comparisons also were made separately in each age-sex subgroup. The only exception was that normotensive men over the age of 50 tended to have a somewhat higher serum sodium than their hypertensive counterparts. It should be noted that there were no normotensive women age 50 or over in the study. In the normotensive group and in the hypertensive group, there was no association between systolic, diastolic, or mean blood pressure and the serum sodium, serum potassium, or sodium to potassium ratio (table 3A).

Stated Salt Intake

As shown in table 3B, relationships were sought between salt intake (determined by Dahl's questions) and the other major variables measured. No association was found between the stated salt intake and, (a) the mean blood pressure, (b) a past history of increased blood pressure, (c) the serum sodium level, or (d) the potassium level.

Table 3

Analysis of Factors

Factors	Group of subjects	Chi-Square	Degrees of freedom	p
A. *Serum electrolytes*				
Mean blood pressure level and serum sodium concentration	Normotensive Hypertensive	(Exact test) 1.431	– 1	Not significant $0.20<p<0.30$
Systolic blood pressure level and serum sodium concentration	Normotensive Hypertensive	(Exact test) 0.420	– 1	Not significant $0.50<p<0.75$
Diastolic blood pressure level and serum sodium concentration	Normotensive Hypertensive	0.039 0.424	1 1	$0.75<p<0.90$ $0.50<p<0.75$
Mean blood pressure level and serum potassium concentration	Normotensive Hypertensive	(Exact test) 0.003	– 1	Not significant $0.950<p<0.975$
Systolic blood pressure level and serum potassium concentration	Normotensive Hypertensive	(Exact test) 1.284	– 1	Not significant $0.25<p<0.50$
Diastolic blood pressure level and serum potassium concentration	Normotensive Hypertensive	0.644 0.593	1 1	$0.25<p<0.50$ $0.25<p<0.50$
Mean blood pressure level and serum sodium-potassium concentration ratio	Normotensive Hypertensive	(Exact test) 0.000+	– 1	Not significant $0.975<p<0.990$
Systolic blood pressure level and serum sodium-potassium concentration ratio	Normotensive Hypertensive	(Exact test) 0.048	– 1	Not significant $0.75<p<0.90$
Diastolic blood pressure level and serum sodium-potassium concentration ratio	Normotensive Hypertensive	(Exact test) 0.074	– 1	Not significant $0.75<p<0.90$
B. *Stated Salt Intake*				
Stated salt intake and mean blood pressure level	Normotensive Hypertensive	(Exact test) 0.224	– 1	Not significant $0.60<p<0.70$
Stated salt intake and a past history of high blood pressure	All	1.166	2	$0.50<p<0.60$
Stated salt intake and serum sodium concentration	All	0.668	2	$0.70<p<0.80$
Stated salt intake and serum potassium concentration	All	9.477	8	$0.30<p<0.40$
Stated salt intake and a family history of hypertension	All	2.377	2	$0.30<p<0.40$

p Indicates the probability of observing a Chi-square as large as or larger than that actually observed when there is no association in the population from which these measurements were drawn.

The "exact test" is used whenever frequencies are too small to permit the valid application of Chi-square. (See *Biometrika Tables for Statisticians:* Eds., E. S. Pearson and H. O. Hartley, Vol. I. Cambridge University Press, 1956, p. 65). The words "not significant" used in connection with this test indicate that the corresponding association fails to approach the 5 per cent significance level.

Other Factors

Chi-square tests for associations between various factors were generally done separately for the normotensive and hypertensive groups. There was no association between sex and serum sodium in either group. Age also was not related to serum sodium or to systolic blood pressure in the two groups. There was a slight tendency toward an association of systolic blood pressure and age within the hypertensive group, but this failed to reach statistical significance. Diastolic blood pres-

Table 4

Results of Present and Prior Studies

Study	Serum sodium (mEq./L.)		Serum potassium (mEq./L.)	
	Normotensive	Hypertensive	Normotensive	Hypertensive
Present study	142.2 ± 4.73 (57)	141.0 ± 4.05 (47)	4.93 ± 0.32 (55)	4.86 ± 0.30 (48)
Holly, Elliot, Holland[4]	144.8 ± 3.81 (400)	147.3 ± 4.07 (75)		
Albert, Morita, Iseri[6]	142 ± 3.0 (43)	147 ± 5.0 (26)	4.06 ± 0.32 (43)	4.23 ± 0.55 (26)
Mathur & Wadhawan[7]	139.2 ± 7.6 (50)	144.4 ± 9.9 (30)	4.6 ± 0.61 (50)	4.4 ± 0.59 (30)
Weller[8]	143 ± 4.05 (11)	142 ± 6.08 (26)		
Winer,[9] Kirkendall et al.[10]	No difference noted			
Hilden & Krogsgaard[11]				Lowered in severe hypertension

Electrolyte values given as the mean ± standard deviation with number of subjects studied in parentheses.

sure and age were unrelated in the normotensive group, but a significant association was present in the hypertensive group. Neither serum sodium nor systolic or diastolic blood pressure was related to height-weight index in either group.

Discussion

A change in electrolyte balance across the cell wall could influence arteriolar resistance either by causing swelling of the cells (increased sodium within the cells), or by altering the membrane potential (a change in K^+_I/K^+_O ratio) and increasing sensitivity to neurogenic or vasopressor stimuli. Many studies have been carried out to evaluate the pathogenetic role of abnormal electrolyte metabolism in essential hypertension, but the results have not been consistent. This is reflected in previous evaluations of the serum sodium and potassium, which are summarized in table 4. Some showed a significant difference in serum sodium and potassium between normal and hypertensive individuals. It was thought that this type of study should be repeated to be certain that such differences were due to the presence of high blood pressure alone and not to the numerous variables. Therefore, as complete data as possible were collected on each patient. Normal and hypertensive subjects were studied simultaneously, and sera from both groups were analyzed at the same time in our own laboratory. Moreover, the serum electrolyte levels were studied in relation to actual blood pressure values, rather than to merely the presence or absence of hypertension.

It should be noted that the hypertensive patients included in the present investigation were rigidly screened, and no patient with any cardiac, renal, or cerebral complication was included. There were no cases of malignant hypertension. Perhaps the patients studied here had less severe hypertensive disease than those reported by some investigators. The range of systolic blood pressure up to 220 mm. mercury and diastolic up to 140 mm. mercury would seem to be sufficient, however, to show association to serum electrolyte levels if one did exist. Statistical analysis of our data disclosed no significant relationships between blood pressure and these electrolyte concentrations. The small Chi-square values found in many of our analyses do not indicate absolutely no association in the larger population of individuals from which subjects are selected, but in conjunction with large p values, they suggest that true associations must be small.

Each patient in this study was asked: "Do you salt your food (a) before tasting, (b) after tasting, or (c) not at all." These were the same questions used by Dahl, who found a direct relationship between elevation of the blood pressure and the level of salt intake.[1] The study presented here shows no such relationship. It has been suggested that questions concerning stated salt intake may not lead to accurate appraisal of actual salt intake, and other methods of estimating salt intake have given conflicting results.[12-14] Evidence for an etiologic role of excessive salt ingestion in hypertensive states is cited in a

recent review of ion metabolism in hypertension.[15] Certain population groups appear to have more hypertension and higher salt intakes. Laboratory investigations indicate that high-salt diets will produce hypertension and also will aggravate various forms of experimental hypertension. Complicating this is the observation that high-potassium intake will protect against these effects.[16] If a relationship between salt intake and hypertension exists, it is a highly complex one.

Summary

This study was undertaken to determine if an association exists between blood pressure level and serum sodium or potassium concentration. All methods and measurements were standardized, and variables possibly influencing these factors were analyzed. Since increased salt intake has been postulated as an etiologic factor in essential hypertension, each patient was questioned in this regard.

Fifty normotensive and 43 hypertensive patients were studied. No significant associations were found between the height of the blood pressure, the serum sodium or potassium level, and the stated salt intake.

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For I have learned from much experience that diseases of the worst description may exist within the chest unmarked by any symptoms, and undiscoverable by any other means than percussion alone.—From *On Percussion of the Chest.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 127.

The Surgical Treatment of Ventricular Septal Defect in Infancy

The Technic and Results of Pulmonary Artery Constriction

By ANDREW G. MORROW, M.D., AND NINA S. BRAUNWALD, M.D.

IN PATIENTS with ventricular septal defect who are more than 3 or 4 years of age, an open corrective operation may be carried out with minimal risk if the lesion is not complicated by the presence of severe pulmonary hypertension. With surgical technics presently available, however, the closure of a ventricular septal defect in an infant or very young child is associated with considerable hazard. In 41 children under the age of 2 operated upon by Cooley[1] the mortality was 39 per cent and in Kirklin's experience in 1956, quoted by Keith,[2] 70 per cent of children in this age group died after open repair. Thus, it seems clear that elective operations for ventricular septal defect should, whenever possible, be deferred until the child has reached optimal age and size.

Although isolated ventricular septal defect is generally considered to be one of the more benign congenital cardiovascular malformations, a certain proportion of infants with this lesion develop severe symptomatology and in this group the early mortality is high. Keith, for example, observed a series of 111 symptomatic children with ventricular septal defect; more than one third died in the first year of life.[2] Seventeen patients who evidenced heart failure were reported by Morgan et al.[3] and, of these, 10 died before the age of 1 year. Marquis[4] found that ventricular septal defect was the most common cause of death from congenital heart disease among children less than 3 years of age.

It is thus apparent that a large number of infants with ventricular septal defect will not survive with nonoperative management and yet should not be subjected to corrective operation because of the prohibitive risk associated with this procedure at the present time. Death in such infants usually results from congestive heart failure often complicated by repeated and severe pulmonary infections. Both are clearly attributable to excessive pulmonary blood flow. Muller and Dammann[5, 6] reasoned that the artificial production of pulmonic stenosis should be beneficial, since children with ventricular septal defect and pulmonary stenosis (e.g., tetralogy of Fallot) ordinarily do well through early childhood. A modification of the operative procedure described by Muller and Dammann has been utilized at the National Heart Institute in the surgical treatment of 13 infants with ventricular septal defect. The criteria utilized in selecting patients for pulmonary artery constriction, the operative method employed, and the results of the procedure are described in the present report.

From the Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

Clinical and Hemodynamic Findings

The 13 children ranged in age from 3 to 22 months (mean 6.5 months) and weighed from 2.6 to 9.8 Kg. (mean 4.7 Kg.). Each had failed to grow and develop normally, and the weight of every patient was below the third percentile in comparison with normal children of the same age and sex. All had experienced repeated episodes of pneumonia and congestive heart failure and the majority of the children had spent most of their lives in hospitals. All were receiving digitalis when first seen. On physical examination they appeared chronically ill and markedly underdeveloped. Gross cardiac enlargement was evident in each, and the typical precordial systolic thrill and murmur of ventricular septal defect were present. The second heart sound in the pulmonary area was always accentuated.

Right heart catheterization was carried out

Table 1

*Summary of Hemodynamic Data in 13 Children Undergoing Pulmonary Artery Constriction**

			Preoperative catheterization				Operative pressures after constriction		
Patient	Age (months)	Weight (Kg.)	Pa* S/D mean	RV*	FA*	Pulmonary/ systemic flow ratio	PA S/D mean	RV	Systolic gradient
R.B.	3	3.9	75/10, 45	90/0	75/45	1.2/1	30/10, 22	60/2	30
C.C.	5	5.6	60/10, 28	60/0	70/36	5.5/1	46/6, 23	100/2	54
S.D.	8	5.1	85/40, 60	85/5	95/60	1.3/1	50/15, 30	85/4	35
R.F.	4½	3.3	65/26, 40	70/10	100/60	3.0/1	45/25, 37	75/15	30
J.M.	22	9.2	60/20, 40	60/0	70/40	2.2/1	30/18, 22	85/4	55
L.R.	4	2.6	—	70/5†	80/60	—	45/20, 32	75/2	30
W.V.	21	9.8	55/24, 30	57/7	112/70	3.7/1	40/25, 35	100/4	60
K.W.	10	4.8	50/16, 40	56/10	90/40	2.5/1	50/25, 40	100/5	50
J.P.	6	3.6	105/55, 80	105/20	100/50	2.3/1	42/21, 36	92/10	50
P.P.	3½	3.5	75/20, 50	75/10	—	—	55/40, 46	95/30	40
J.J.	8	3.5	65/25, 40	65/2	70/40	3.5/1	25/10, 20	70/4	45
S.G.	3	3.2	100/60, 68	105/12	—	3.1/1	28/12, 20	60/6	32
R.M.	5	2.7	40/15, 26	40/0	70/36	1.9/1	25/15, 20	110/4	85

*PA, RV, and FA refer to pulmonary arterial, right ventricular, and femoral arterial pressures, respectively. The systolic (S), diastolic (D), and mean pulmonary arterial pressures are listed. All pressures are in mm. Hg.

†Operative pressure measurement, no preoperative catheterization.

in 12 of the 13 children; these data are summarized in table 1. In every instance the presence of a left-to-right shunt entering the right ventricle was demonstrated by the nitrous oxide test, serial blood oxygen determinations, or indicator-dilution curves. Pulmonary arterial and right ventricular hypertension was uniformly found, and the ratio between the pulmonary arterial and systemic arterial pressures was 66 per cent or more in nine of the 10 patients in whom both measurements were made.

In every patient it was the opinion of the staff and the referring pediatrician that unless immediate operative treatment was undertaken the infant would not survive to an age at which the ventricular septal defect could be closed.

Operative Technic

Anesthesia is ordinarily induced with cyclopropane and maintained with nitrous oxide and oxygen while respiration is controlled with succinylcholine. The saphenous vein is cannulated at the ankle for the administration of fluids and blood. The patient is placed on the table in the supine position with the left side slightly elevated. A left anterolateral thoracotomy through the fourth intercostal space is employed (fig. 1.). The lung is first retracted anteriorly and the region of the ductus arteriosus dissected. It is usually difficult to determine the patency of a small ductus but the structure is always ligated. The pericardium is then incised anteriorly, exposing the main pulmonary artery and right ventricle. The pleural reflection between the aorta and main pulmonary artery is incised, and the pulmonary artery is freed until an angled clamp can be passed beneath it. A strip of Nylon cloth 1 cm. in width is then drawn about the vessel. Control pressure measurements are then made in the right ventricle and pulmonary artery by means of 20-gage needles attached through sterile connecting tubes to equisensitive Statham pressure transducers. The cloth band is then tightened with a clamp until a vigorous thrill is palpable distal to it (fig. 2). While this degree of constriction is maintained by the clamp, the right ventricle and pulmonary arterial pressures are again measured. The constriction is adjusted until the mean pulmonary artery pressure is reduced to approximately 20 to 30 mm. Hg. The systolic gradient between the right ventricle and distal pulmonary artery will ordinarily be 30 to 50 mm. Hg at this time. When the desirable degree of constriction is achieved the heart action is observed for several minutes and if no detrimental effect is apparent the tape is sutured to itself beneath the clamp (fig. 3). Care must be taken that the sutures do not pierce the wall of the pulmonary artery. Following completion of the constriction, confirmatory pressure measurements are again made. The final operative pressure measurements

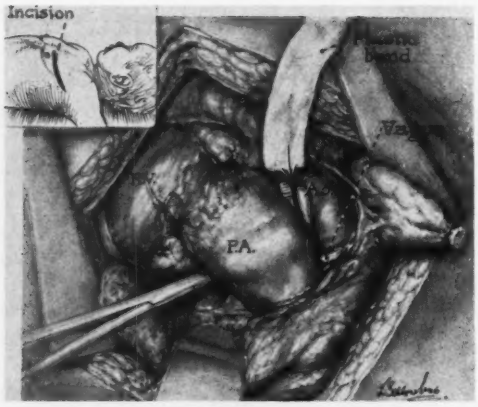

Figure 1

Operative method for pulmonary artery constriction. After ligation of the ductus or ligamentum arteriosus, the pulmonary artery is freed from the aorta, and the Nylon band is passed beneath it.

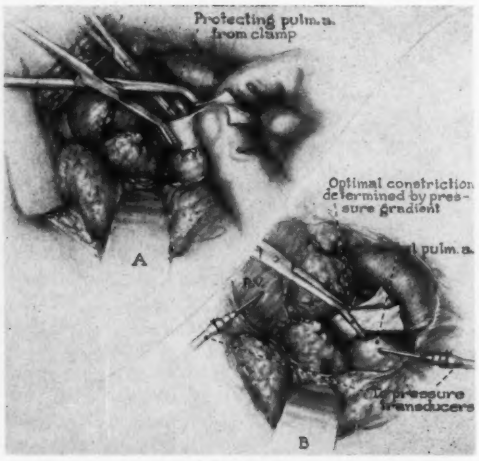

Figure 2

The constriction is initially produced by securing the band with a clamp and its degree is adjusted as proximal and distal pressure measurements are made.

in all patients are listed in table 1, and representative tracings obtained in patients C.C. and S.G. are reproduced in figures 4 and 5. Postoperative management is usually not difficult. The usual precautions must be taken to insure that tracheobronchial secretions are evacuated and oral feedings are begun 12 hours after operation.

Results

Of the 13 infants with ventricular septal defect subjected to pulmonary artery constriction 12 are living and well. The one death occurred in patient P.P. She appeared to tolerate the operative procedure well but died suddenly 36 hours afterward. It was considered likely that she aspirated a feeding but this could not be established at autopsy and no specific cause for her death was apparent. The presence of a large ventricular septal defect was confirmed at this examination.

The 12 surviving patients have been followed for periods of 9 months to 4 years. With one exception each has shown striking improvement in growth and development and all have increased exercise tolerance. The weight of each patient before operation and at successive clinic visits has been plotted by percentiles according to the anthropometric charts constructed at the Children's Medical Center, Boston. These data for the 10 children who have been followed for 20 months or longer are reproduced in figure 6. With the exception of patient R.M. each has shown excellent weight gain. Improvement following operation has occurred at a variable rate but in general maximum benefit has become apparent only after a period of 6 to 12 months.

Clinical evidences of congestive heart failure have disappeared in every patient postoperatively, and the administration of digitalis has been discontinued in the majority of them. The children have all experienced upper respiratory infections but none has had pneumonia. It was considered that cyanosis might become apparent as the children became older but this has not been evident in any thus far. Every patient continues to have the murmur of ventricular septal defect and in addition a loud ejection murmur and often a thrill are present over the pulmonary area. The hearts of all patients are still enlarged on x-ray examination. None has, as yet, been catheterized postoperatively.

Clinical Example

A brief clinical summary of patient R.F. is presented to illustrate the typical findings and the course of a patient subjected to pulmonary artery constriction.

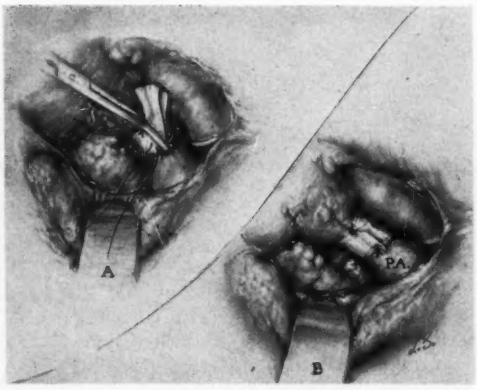

Figure 3

When the optimal degree of constriction has been achieved the band is sutured to itself beneath the clamp and the pressures are again measured. The degree of constriction can be increased, if necessary, by the placement of additional sutures.

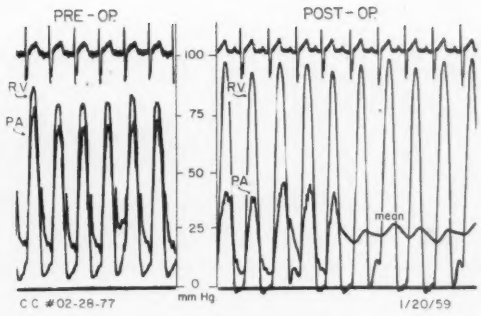

Figure 4

Operative records of right ventricular and distal pulmonary arterial pressures in patient C.C. before (left) *and after* (right) *pulmonary artery constriction.*

R.F. (02-01-10) was a male infant whose birth weight was 2.5 Kg. He was apparently well until the age of 2½ months, when severe dyspnea with feedings was noted and he developed a chronic cough. At this time a heart murmur was heard and congestive heart failure was evident. He was said to have been cyanotic on several occasions and had been hospitalized repeatedly for severe respiratory infections. He had gained weight poorly since birth and when admitted to the National Heart Institute at the age of 5½ months he weighed only 3.3 Kg.

On examination he was obviously cachectic (fig. 7A). The heart was enlarged, and a systolic thrill was felt in the third left intercostal space. The second heart sound in the pulmonary area was loud and a grade 3/6 systolic murmur was audible all over the precordium and was loudest along the left sternal border. There were moist rales at both lung bases and the liver was palpable 4 cm. below the costal margin. By x-ray the heart was seen to be grossly enlarged and the pulmonary vascularity was markedly increased. The electrocardiogram revealed right axis deviation and right ventricular hypertrophy. At right heart catheterization (table 1) there was found to be severe right ventricular and pulmonary arterial hypertension. Nitrous oxide indices of 66, 65, and 8 per cent in the pulmonary artery, right ventricle, and right atrium, respectively, indicated that a large left-to-right shunt entered the right ventricle.

The child was considered to be an ideal candidate for pulmonary artery constriction and the operation was performed in December 1957. A ductus 2 mm. in diameter, and questionably patent, was found and ligated. The pulmonary artery was constricted until the mean pressure distally was reduced to 30 mm. Hg and a systolic gradient of similar magnitude had been produced. Postoperatively his course was smooth and he immediately began to take much larger feedings; in the first 12 postoperative weeks he gained 1.1 Kg. After 1 year his development and weight gain continued to be rapid (fig. 7B) and by the age of 2½ years both his height and weight were greater than the fiftieth percentile on the anthropometric chart. He has never evidenced cyanosis, dyspnea, or fatigability on unrestricted activity. The typical ejection murmur of pulmonic stenosis is audible. The electrocardiogram and relative size of the heart x-ray have remained essentially unchanged, although some decrease in pulmonary vascularity is apparent.

Discussion

The prognosis in a newborn infant with a ventricular septal defect is, in general, dependent upon the size of the communication and the pulmonary vascular resistance. If the defect is small the shunt and the resultant extra burden on the left ventricle will usually not be sufficient to cause symptoms or failure. If, on the other hand, the defect is of large size and approximates the aortic orifice, it will offer little resistance to the flow of left ventricular blood, and the magnitude of the shunt is limited only by the resistance in the pulmonary vascular bed. If the circulation of an infant with a large ventricular septal defect can adjust to the increased pulmonary blood flow soon after birth, presumably by the

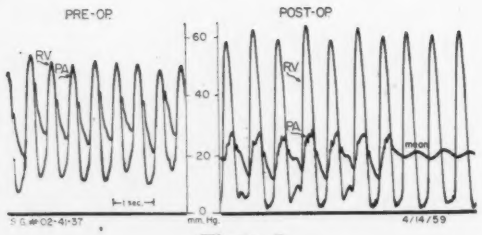

Figure 5

Operative records of right ventricular and distal pulmonary arterial pressures in patient S.G. before (left) *and after* (right) *pulmonary artery constriction.*

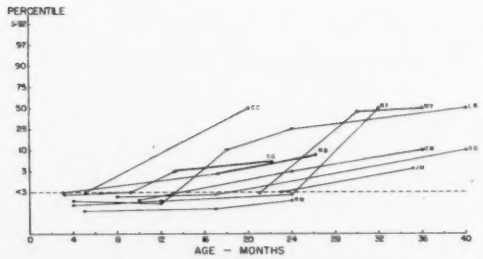

Figure 6

The weights of 10 children before and at intervals after pulmonary artery constriction. They are expressed as percentiles according to the anthropometric chart constructed at the Children's Medical Center, Boston.

development of increased pulmonary vascular resistance, survival is possible. If such adjustment is not made failure will certainly ensue and the risk of death within the first months of life will be high. The operation of pulmonary artery constriction artificially produces increased resistance to right ventircular ejection but does so proximally and in a reversible manner. It is likely that the medial hypertrophy of the pulmonary arterioles is related to increased pulmonary blood flow and high pulmonary arterial pressure. Thus pulmonary artery constriction may also be found helpful in preventing or ameliorating the development of these changes, considered by some to be irreversible.

When operative treatment is contemplated in an acyanotic infant presenting congestive failure, first consideration must be given to the establishment of the correct diagnosis. If the shunt is primarily into the right atrium rather than into the right ventricle, as in the incomplete form of persistent atrioventricular canal, pulmonary artery constriction will be of little benefit, since reduction of the magnitude of the shunt could result only at the expense of right ventricular failure with elevation of the right ventricular end-diastolic and right atrial pressures. These considerations may explain why patient R.M. has not experienced so great benefit as the other patients. In addition to a ventricular septal defect he also was shown to have an interatrial communication and a moderate-sized shunt into the right atrium. Thus cardiac catheterization would seem to be indicated preoperatively in every patient. When the diagnosis of ventricular septal defect is made by catheterization, the results of the study are usually of little further aid in determining the necessity for pulmonary artery constriction, and this decision must rest largely on clinical considerations.

The selection of patients for the operation is usually not difficult. The procedure ordinarily is indicated in an infant with ventricular septal defect under the age of 12 to 18 months when weight gain is poor, or at a standstill, and when failure and infection have not responded to intensive pediatric management over a prolonged period of hospitalization. When failure responds to digitalization and respiratory infections can be effectively controlled by the use of antibiotics, operative treatment can likely be deferred until an open corrective procedure can be performed with relative safety.

It has been suggested that the correct degree of constriction of the pulmonary artery can be determined by inspection alone. In our experience the mere appearance of the narrowed segment may be quite misleading, and physiologic control has been found to be essential. When the first pulmonary artery constrictions were performed in this clinic, attempts were made to regulate the degree of constriction not only by the measurement of proximal and distal pressures but also by ear oximetry. It was considered that optimal constriction might be the point at which a

small right-to-left shunt first occurred, signaled by a slight reduction in peripheral arterial oxygen saturation. This technic was found unsatisfactory and was abandoned because of the great respiratory variations recorded by the oximeter; pressure measurements alone are now used.

The immediate object of the operation is to reduce pulmonary blood flow, and this of course is necessarily accompanied by a fall in pulmonary arterial pressure. Since the flow through the pulmonary vascular bed is directly proportional to the difference between the pulmonary arterial and left atrial pressures, the reduction in flow can easily be estimated. In the present series the average reduction in mean pulmonary arterial pressure was about 15 mm. Hg and the average reduction in pulmonary flow was approximately 33 per cent. To accomplish a constriction of this degree, which by experience seems satisfactory, the area of the lumen of the artery must be narrowed to nearly one third of its original diameter. It should be emphasized that the pressure measurements must be made while the action of the heart is vigorous. Often in the course of the operation, particularly when the pulmonary artery is being freed or when the band is initially tightened, the heart will slow and its contractions become feeble. Under these circumstances small doses of intracardiac calcium chloride (0.5 to 1.0 ml. of 10 per cent solution) ordinarily restore vigorous heart action, and this drug was necessary in many of the patients described. The above considerations would seem to indicate that the pulmonary artery, under optimal conditions, should be narrowed sufficiently to effect a reduction of 30 to 40 per cent in the mean pulmonary arterial pressure. This will ordinarily result in a systolic gradient between the ventricle and distal pulmonary artery of about 50 mm. Hg and the diameter of the artery will be reduced by about two thirds.

The operation described is, of course, a palliative one and a later definitive procedure will be necessary. Both experimental studies[7] and isolated clinical reports[8, 9] indicate that the stenosis produced by constriction of the pulmonary artery by a cloth band can be

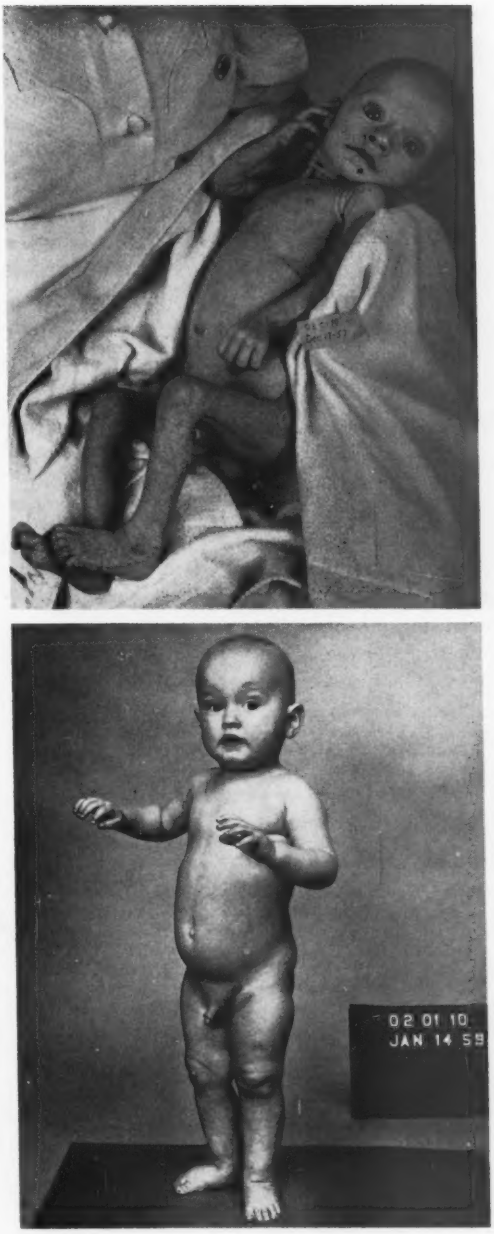

Figure 7

Patient R.F. immediately (top) *and 1 year* (bottom) *following pulmonary artery constriction.*

relieved without undue difficulty at the time the ventricular septal defect is closed.

The gratifying clinical benefit evidenced by the children described in this report is reinforced by similar results in other clinics.[10-12] It would seem that pulmonary artery constriction will remain the surgical procedure of choice in infants with ventricular septal defect and heart failure until the technics of the open operation are sufficiently refined to permit an initial corrective operation at an acceptable risk.

Summary

Thirteen infants with ventricular septal defect, pulmonary hypertension, and severe congestive heart failure were treated by pulmonary artery constriction. The 12 children who survived operation have been followed from 1 to 4 years and have evidenced striking improvement in growth, weight gain, and exercise tolerance. None has had pneumonia or heart failure after operation. Considerations in the selection of patients for pulmonary artery constriction, the surgical method employed, and its hemodynamic control are described.

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The effect of effused fluids in producing the morbid sound is at once proved by the injection of water into the thorax of a dead body; in which case it will be found that the sound elicited by percussion will be obscure over the portion of the cavity occupied by the injected liquid.—From *On Percussion of the Chest.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 129.

A Histopathologic Study of the Atrioventricular Communications in Two Hearts with the Wolff-Parkinson-White Syndrome

By Maurice Lev, M.D., Rexford Kennamer, M.D., Myron Prinzmetal, M.D., and Quintiliano H. de Mesquita, M.D.

THE ANATOMIC BASE as studied at autopsy of the electrocardiographic arrhythmia, the Wolff-Parkinson-White syndrome, also variously called "accelerated conduction," "preexcitation," and "double atrioventricular conduction" is today fragmentary. The atrioventricular communications of only a few hearts with this abnormality have been studied histologically in the past. In them either only the conduction system, or accessory communications outside the conduction system have been studied. In one case of Ebstein's disease, however, Lev, Gibson, and Miller[1] studied all possible muscular atrioventricular communications. In a recent case of myocarditis, Truex, Bishof, and Downing[2] made a similar study reenforced by a wax model reconstruction of the atrioventricular muscular communications.

As pointed out previously[1] a proper study of the anatomic base of this disturbance must entail a study by serial sections of the atrioventricular orifices and of the entire conduction system, and an adequate study of the entire atrial and ventricular myocardium. Such a study was undertaken by us in two hearts (with the exception of the sinoatrial (SA) node in one heart) diagnosed electrocardiographically as having the WPW syndrome.

From the Congenital Heart Disease Research and Training Center, Hektoen Institute for Medical Research, the Departments of Pathology of Northwestern University Medical School, and The University of Chicago School of Medicine, Chicago, Illinois, the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, California, and the Cardiovascular Institute of the Matarazzo Hospital, São Paulo, Brazil.

Supported by a grant from the American Heart Association and by grants (H-3440 and H-3351) from the National Heart Institute, U. S. Public Health Service.

Materials and Methods

The parietal wall of the right atrioventricular ring and the entire atrioventricular junction of the atrial and ventricular septum beginning at the region of the Eustachian valve and ending at the muscle of Lancisi were serially sectioned at 10 μ. The sections contained the approaches to the atrioventricular (AV) node, the AV node, the AV bundle, and a considerable part of the bundle branches. The parietal wall of the left atrioventricular ring and the distal part of the ventricular septum up to the moderator band were similarly sectioned, but only every tenth section was retained. The remainder of the atria and ventricles was cut into blocks and two sections were made of each block. The Péter, double-embedding method was used in all blocks with the exception of the atrioventricular junctions on the septal surface, which were embedded in paraffin. Every fifth or tenth section was stained with Weigert-van Gieson stain. The other sections were stained with hematoxylin-eosin stain. In this way 9,405 sections were studied in the first heart, and 7,830 sections were studied in the second heart. Forty-eight and 27 sections were lost in the serial sectioning in these hearts, respectively.

Case Reports

Case 1

This 37-year-old male Brazilian farm worker complained of progressive dyspnea on effort, eventually accompanied by orthopnea, edema of the lower extremities, ascites, and asthenia of 2 months' duration. These symptoms were accompanied by crises of tachycardia of sudden onset, appearing both spontaneously or after effort.

The patient lived in a region infested with Triatoma carriers of Chagas' disease *(Trypanosomiasis cruzi)*. No complement fixation test was made for Chagas' disease, however; and serologic tests for syphilis were negative. The patient denied having had rheumatic fever.

Physical examination revealed a blood pressure

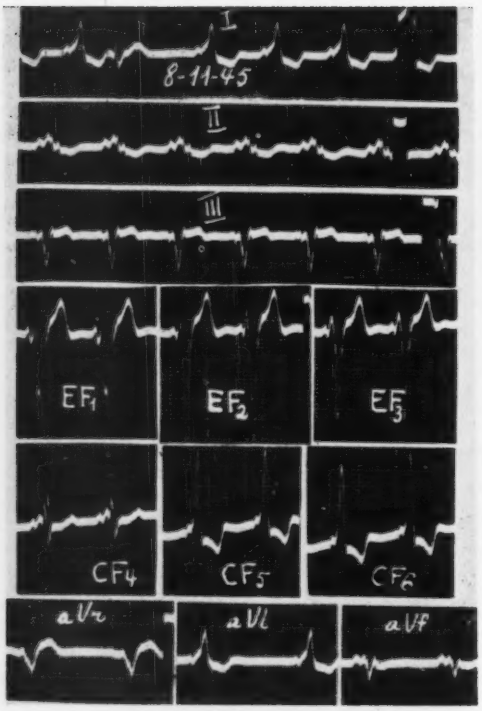

Figure 1

Case 1. Electrocardiogram showing WPW syndrome with pattern of left bundle-branch block.

of 108/78 mm. Hg. The maximum cardiac impulse was in the sixth left intercostal space outside the midclavicular line. A slight systolic murmur at the aortic area was not propagated. There was a gallop rhythm. The liver was enlarged four fingers below the costal margin and was painful to palpation. Fluid was present in the abdomen.

An electrocardiogram showed sinus rhythm and the Wolff-Parkinson-White syndrome with pattern of left bundle-branch block (fig. 1).

During his stay the patient did not respond to treatment. Intravenous injection of 1 mg. of atropine did not alter the WPW syndrome. He died 1½ months after entry into the hospital. The clinical diagnosis was aortic stenosis with possible chronic Chagas' myocarditis.

Only the heart was available for postmortem examination. It was enlarged and weighed 510 Gm. The proximal part of the atria including the SA nodal region was not present in the specimen. The right atrium was thickened. The right ventricle was normal in size, but its wall was markedly thickened (0.4 to 0.7 cm.).

The left atrium was increased in thickness. The

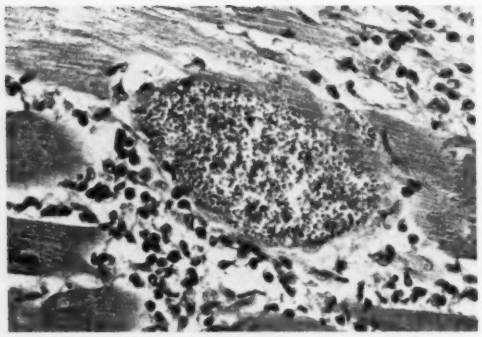

Figure 2

Case 1. Chagas' myocarditis with Leishmania, apparently in muscle cell. Hematoxylin-eosin stain.

left ventricle was enlarged, and its wall was thickened (1.5 cm.). The aortic orifice measured 5.8 cm. in circumference at its base but 3 to 4 cm. at the valve margin. The aortic valve consisted of right, and incompletely divided left and posterior cusps, which were markedly thickened. The coronary arteries showed minimal sclerotic change and no narrowing.

On *microscopic examination,* in general, there were focal accumulations of lymphoid cells, macrophages, and plasma cells, with few neutrophils dispersed throughout the myocardium. Nerve trunks were infiltrated with lymphoid cells, especially in the atrial septum. The vessels showed acute vascular degeneration, and there was focal irregularity in staining of the myocardial fibers. Some of the arterioles were considerably thickened. In the left ventricle and minimally in the right, there was considerable fibrosis with small subendocardial and occasional subepicardial scars. In the left ventricle, in addition, there were foci of neutrophils, occasionally forming small abscesses. Also, peculiar granulomas consisting of mononuclear cells and occasional giant cells surrounded masses of swollen collagen in the left ventricle. Here also there were some tremendously swollen myocardial cells, and some contained Leishmania (fig. 2).* Also, typical recent and organizing infarcts permeated the left ventricle and septum with zones of hemorrhage. Some large microscopic coronary arteries and occasional small ones contained recent thrombi.

Focally the endocardium and subendocardium of both atria and ventricles were infiltrated with lymphoid cells and occasional neutrophils and showed a swelling of their lining cells. Recent and organizing mural thrombi covered portions

*I am indebted to Dr. William C. Manion for verifying the identity of the organisms.

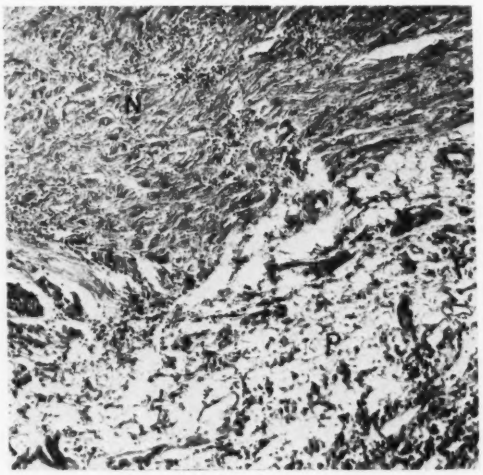

Figure 3

Case 1. Beginning of AV node and perinodal region, showing marked infiltration of lymphoid cells. Hematoxylin-eosin stain. N, AV node; P, perinodal tissue.

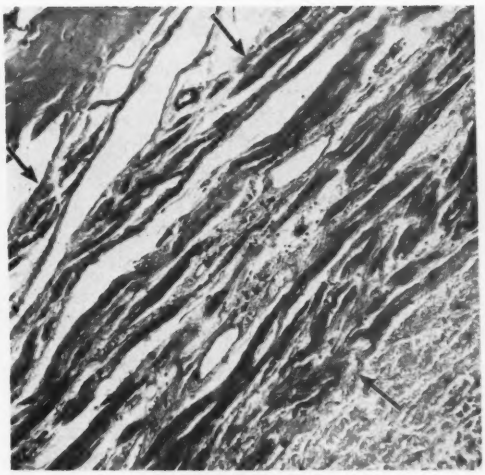

Figure 4

Case 1. Longitudinal section through the penetrating portion of the AV bundle, showing infiltration of lymphoid cells. Hematoxylin-eosin stain. Arrows point to the bundle.

of it in the right atrium and both ventricles. Focal endocardial hypertrophy was marked in the left ventricle and left atrium.

The annulus and adjacent fibrosa of all valves was infiltrated with lymphoid cells. The proximalis and distalis layers focally were infiltrated with lymphoid cells and were proliferated. The aortic valve in addition showed a marked proliferation of elastic and collagenous tissue, with disruption of the fibrosa and spongiosa, degenerative changes, and calcification.

There was an infiltration of lymphoid cells in the epicardium with fat necrosis and acute vascular degeneration.

Conduction System. The approaches to the AV node showed a marked infiltration of lymphoid cells with degenerative and necrotic changes of fat tissue. The periphery of the AV node was also markedly infiltrated with lymphoid cells (fig. 3). The center of the node and the penetrating portion of the bundle were moderately infiltrated with lymphoid cells (fig. 4), and there were degenerative changes in the bundle. The branching portion of the bundle showed only slight infiltration of lymphoid cells. The bundle was relatively short. The first and second portions of the right bundle branch were moderately infiltrated with and surrounded by lymphoid cells. The third portion was markedly infiltrated with lymphoid cells and occasional neutrophils. The beginning of the left bundle branch was normal. Progressively downward, however, the left bundle branch became

Figure 5

Case 1. Peripheral portion of Purkinje fibers of left bundle branch, showing infiltration of lymphoid cells and degenerative changes in the Purkinje cells. Hematoxylin-eosin stain. Arrows point to the left bundle branch. M, adjacent myocardium.

markedly infiltrated with lymphoid cells and occasional neutrophils (fig. 5), and the Purkinje cells showed marked degenerative changes with a proliferation of fibroblasts. These inflammatory changes were very marked at the junction of the Purkinje cells with the myocardium.

The only Mahaim fibers found were small communications at the beginning of the left bundle branch. Some fascieuli passed from the right bundle branch downward into the septum but did not anastomose with the myocardium.

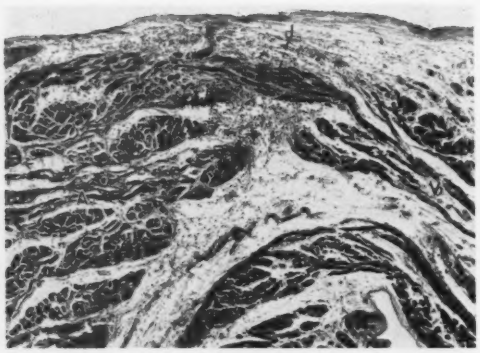

Figure 6

Case 1. Muscular communication between right atrium and right ventricle with an infiltration of lymphoid cells. Hematoxylin-eosin stain. A, atrial musculature; V, ventricular musculature; J, junction muscular tissue.

Right Atrioventricular Orifice. Numerous small and large muscular communications extended over a distance of 0.52 cm. between the endocardial portions of the musculature of the right atrium and ventricle in the lateral wall (fig. 6). The largest of these communications measured 0.76 mm. These communications consisted of ordinary cardiac musculature, and were surrounded by masses of lymphocytes.

Left Atrioventricular Orifice. There were no muscular communications between the atrium and ventricle.

The pathologic diagnoses were (1) calcific aortic stenosis (probably superimposed on bicuspid aortic valve); (2) chronic Chagas' myocarditis with endocarditis, epicarditis, and involvement of the conduction system; (3) hypertrophy of all chambers of the heart; and (4) muscular communications between right atrium and right ventricle.

Case 2

This 39-year-old white female Brazilian entered the hospital with a 10 years' complaint of tachycardia of sudden onset and end, lasting many hours and even days. During these spells she became dizzy and had vomiting and sweating. She entered the hospital in such a crisis.

The patient came from a region infested with Triatoma carriers of Chagas' disease *(Trypanosomiasis cruzi)*. No complement fixation test for Chagas' disease was made.

Physical examination revealed a blood pressure of 130/90 mm. Hg. The maximum cardiac impulse was in the fifth intercostal space at the midclavicular line.

The electrocardiograms showed atrial paroxysmal tachycardia, and the Wolff-Parkinson-White syndrome during the periods of sinus rhythm. At the end of the tachycardia there was complete right bundle-branch block (fig. 7).

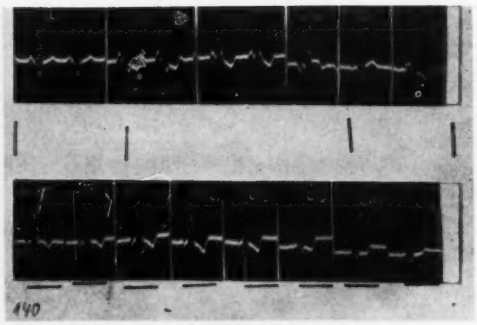

Figure 7

Case 2. Electrocardiogram showing WPW syndrome with right bundle-branch block.

During her hospital stay physiologic rhythm was temporarily established by the oculocardiac reflex. The patient died suddenly, however, on the sixth day.

Only the heart was available for postmortem examination. It weighed 475 Gm. The right atrium was enlarged and thickened (1 to 2 mm.). The right ventricle was markedly enlarged and markedly thickened (0.3 to 0.6 cm.). The pulmonic orifice was larger than the aortic. It was guarded by a valve consisting of a right posterior cusp and a left cusp. The latter was subdivided by a low raphé into left posterior and anterior components. The right posterior cusp was thickened at the commissure between it and the left posterior component of the left cusp. Thickened white longitudinal ridges were noted immediately beneath the commissure in the endocardium of the right ventricle. The pulmonary artery was widened distal to the valve.

The left atrium was larger than the right and its wall was thicker (0.2 to 0.3 cm.). The left ventricular chamber was somewhat enlarged, but apparently smaller than the right and its wall was somewhat thickened (1.4 cm.). The aortic orifice was normal in size (smaller than the pulmonary) and its valve was normally formed. The cusps were irregularly thickened but not retracted. The anterior descending coronary artery was slightly narrowed by atherosclerotic plaques.

On *microscopic examination,* in general, there was a fine infiltration of mononuclear cells, macrophages, lymphoid cells, eosinophils, and neutrophils with a proliferation of young connective tissue and the formation of small scars in the myocardium. Acute vascular degeneration with

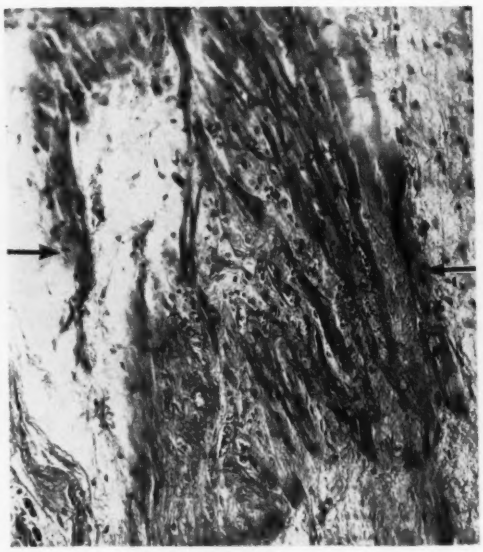

Figure 8

Case 2. Longitudinal section through the periphery of the penetrating portion of the bundle, showing an infiltration of lymphoid cells. Hematoxylin-eosin stain. Arrows point to the bundle.

early necrosis, especially of the small vessels was present throughout. Frequently the small vessels were cuffed by young connective tissue. This basic picture was present in all chambers. This picture was greatly altered in the left ventricle, where there were larger areas of replacement of myocardium by granulomatous and scar tissue. The granulomatous tissue consisted of macrophages, epithelioid cells, and plasma cells with occasional giant cells of the foreign body and of the cardiac muscle type. Here many muscle fibers were in various stages of degeneration and necrosis. No Leishmania could be identified. Some arterioles were markedly thickened in these regions. These areas were mostly in the subendocardial portions, but were also present elsewhere. In the ventricular septum they were more numerous distally. In contrast to this the right ventricle presented only an occasional scar and granuloma, while the atria and the atrial septum showed only the basic picture, but no granulomas.

There was focal thickening of the endocardium in all chambers with fibrinoid necrosis in some areas, and a focal infiltration of neutrophils. In the left atrium, the subendocardium showed scattered macrophages, and the endocardial hypertrophy was diffuse.

The aortic valve showed a proliferation of endothelial cells with an infiltrate of mononuclear cells in the core (spongiosa and fibrosa). In addition, there was marked endocardial hypertrophy and sclerosis with calcification. The pulmonic valve was unfortunately not studied.

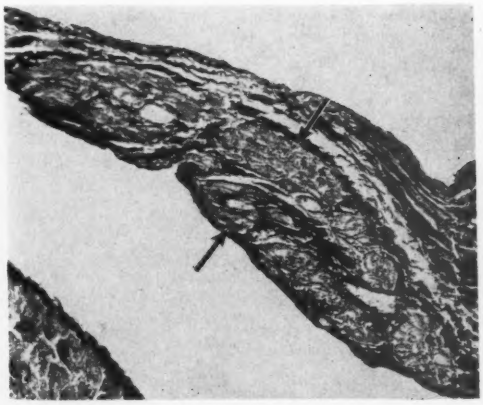

Figure 9

Case 2. Right bundle branch lying in chordal tissue in the lumen of the right ventricle. Weigert-van Gieson stain. Arrows point to the right bundle branch.

In the epicardium there was a focal infiltration of mononuclear cells and neutrophils with acute vascular degeneration and early necrosis. The mesothelial lining was hypertrophied with thickening of the septa around fat cells.

Conduction System. The SA node presented only an occasional lymphocyte. The approaches to the SA node and the adjacent myocardium showed a fine infiltration of mononuclear cells with a considerable diffuse increase in connective tissue. The approaches to the AV node were similarly involved. The proximal part of the AV node showed moderate fibroelastosis but no inflammatory cells. The penetrating portion of the bundle presented scattered neutrophils and lymphoid cells (fig. 8). The branching portion of the bundle showed a moderate infiltration of mononuclear cells on its periphery and in its substance. At the bifurcation and in the beginning of the right bundle branch there was a slight infiltration of mononuclear cells. At the bifurcation the right bundle branch divided into two parts. One part ascended to the conus musculature and stopped blindly. The other part entered a portion of chordal and tricuspid valvular tissue, thus leaving the ventricular septum and traveling in the lumen of the right ventricle until about the region of the muscle of Lancisi (fig. 9). The first portion of the right bundle branch showed no other changes. As it joined the septum again (fig. 10), it became completely fibrotic for a distance of

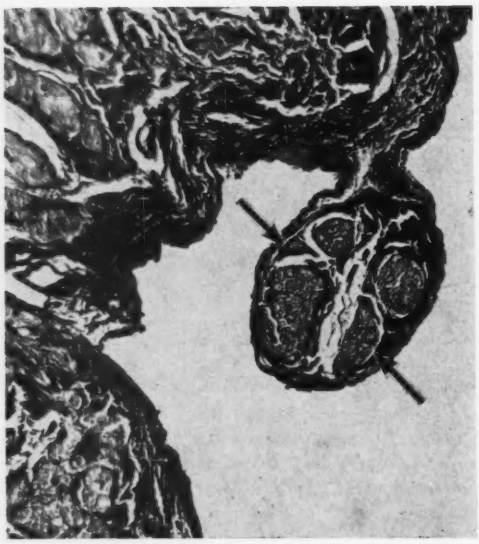

Figure 10

Case 2. Right bundle branch joining the septum again. Weigert-van Gieson stain. Arrows point to the right bundle branch.

about 1 mm. (figs. 11 and 12). Distal to this point it became normal again throughout its second and third portions. In the beginning of the left bundle branch some distance from the bifurcation there was a distinct communication between the posterior radiation and the septum (fig. 13). More distally there was focal necrosis of the left bundle branch, but no infiltration of cells. However, it ran adjacent to large granulomatous areas of myocardium (fig. 14). The ramus septi fibrosi showed no change. The arterioles of the septum were thickened focally.

The only upper connections (Mahaim) found was that of the posterior radiation of the left bundle branch with the myocardium described above. This was perhaps a little bit further down than is usual with Mahaim fibers.

Both Atrioventricular Orifices. There were no communications found between the atria and the ventricles in the atrioventricular sulci.

The pathologic diagnoses were (1) congenital heart disease with bicuspid pulmonic valve with insufficiency, (a) right atrial and ventricular hypertrophy and dilatation, (b) dilatation of the pulmonary artery, (c) abnormal right bundle branch with complete focal fibrosis; (2) chronic granulomatous myocarditis (possible Chagas' myocarditis) with epicarditis and endocarditis with involvement of the conduction system, (a) hypertrophy of the left atrium and ventricle.

Discussion

The various theories for the production of the WPW syndrome must be evaluated in the light of the findings in our cases and the findings of other histologically studied cases in the literature. These theories have been recently reviewed.[3] Prinzmetal et al.[3, 4] believed that there is accelerated conduction along the normal conduction system, produced by lack of delay at the AV node. According to Sodi-Pallares et al.,[3, 5] certain areas in the upper part of the ventricular septum are hypersensitive and easily stimulated, and the stimulus responsible for the excitation of these areas does not travel by an anatomically recognizable pathway. According to Pick and Katz,[3, 6] Segers et al.,[7] Langendorf,[8] Fox,[9] and Harnischfeger,[10] the WPW syndrome is related to accessory conduction pathways bypassing the AV node. According to de Mesquita,[11] the WPW syndrome may be related to an accessory conduction pathway bypassing the node, or acceleration within the conduction system, where the accelerated functional pathway is in competition with the normal functional pathway.

The anatomic studies are fragmentary and reveal the following: Wood and associates[12] found three muscle communications between the right atrium and right ventricle in one case, and Levine and Burge[13] found one such communication in another case Öhnell[14] found a muscle connection between the left atrium and ventricle in one case. Deerhake and associates[15] also found two communications, one on the right and one on the left side. In other cases, Holzmann[16] and Öhnell[17] did not find such communications. These studies, however, did not include studies of the conduction system.

Some workers have studied parts of the conduction system but not other atrioventricular communications. Mahaim and Bogdanovic,[18] found inflammation of the left bundle branch and around the right bundle branch in a case of myocarditis. There were no paraspecific connections between the AV node and bundle and septum. Prinzmetal and

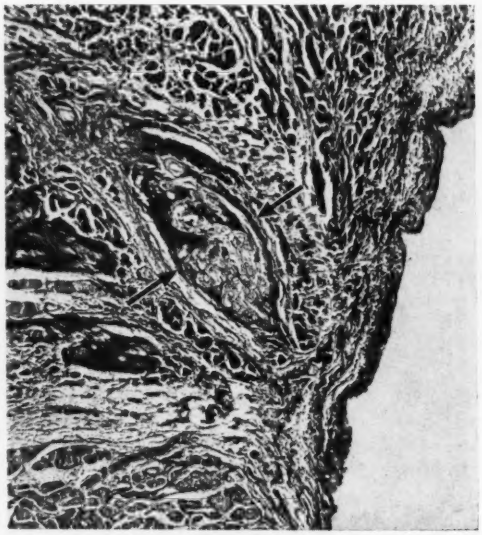

Figure 11

Case 2. Right bundle branch showing moderate fibrosis. Weigert-van Gieson stain. Arrows point to right bundle branch.

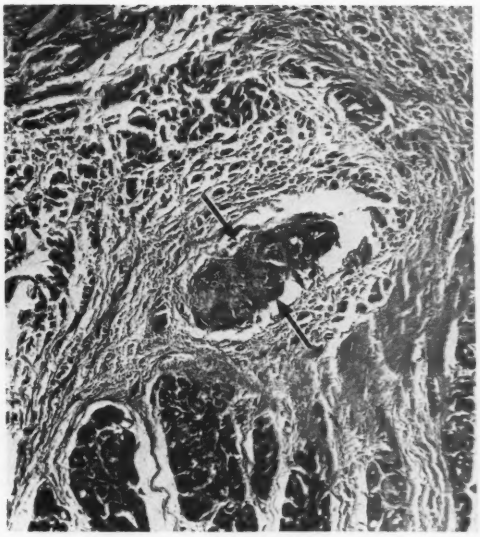

Figure 12

Case 2. Right bundle branch showing complete fibrosis. Hematoxylin-eosin stain. Arrows point to right bundle branch.

associates[3, 4] found pathologic changes in and around the AV node in five consecutive cases. Segers and co-workers found a connection between the AV node and septum. Rossi and Rovelli[19] found what they considered to be an anomalous course of the AV bundle with an inflammatory and sclerotic focus in one case.

Lev, Gibson, and Miller[1] studied all possible muscular conduction pathways in a case of Ebstein's disease. They found (1) a large right atrioventricular communication outside the "conduction system"; (2) in addition to usual Mahaim communications between the node and the penetrating portion of the bundle, there was a small communication between the right bundle branch and the septum; and (3) the right bundle branch was encased in fibroelastic tissue. Likewise Truex, Bishof, and Downing[2] made a similar study coupled with wax model reconstructions of the atrioventricular communications in a case of myocarditis. They found (1) an accessory atrioventricular communication outside the "conduction system"; and (2) chronic inflammation with fibrosis of the SA node and fibrosis of the AV node and left bundle branch.

Furthermore, all these findings must be evaluated with regard to the atrioventricular communications outside the conduction system in the normal heart and in pathologic hearts without the WPW syndrome. Lev and Lerner[20] found no such communications in fetal and newborn hearts. Truex, Bishof, and Hoffman,[21] however, found occasional such communications below the age of 6 months but not after. Edwards[22] found a muscular communication between the right atrium and ventricle in a case of Ebstein's disease without the WPW syndrome. And Mahaim[23] found a communication between the left atrium and ventricle in a case of common ventricle with agenesis of the AV bundle but without the WPW syndrome.

It therefore appears from the study of the literature and of our two cases that the WPW syndrome can occur without accessory muscular connections outside the conduction system, and that it may not be present when such communications do exist. It may also

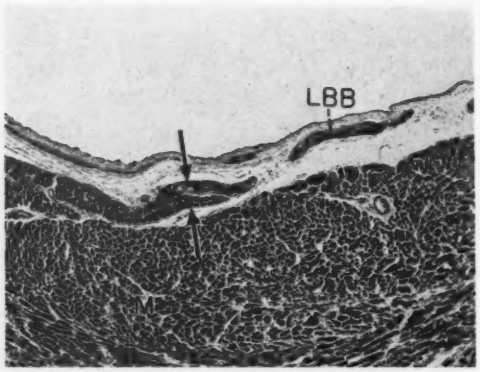

Figure 13

Case 2. Fibers of left bundle branch joining the septum in its upper portion. Hematoxylin-eosin stain. LBB, left bundle branch M, myocardium. Arrow points to junction between left bundle branch and septal musculature.

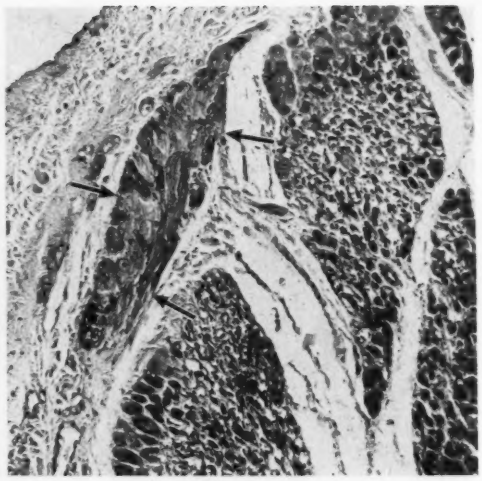

Figure 14

Case 2. Fibers of left bundle branch showing degenative changes and lying adjacent to granulomatous zone of myocardium. Hematoxylin-eosin stain. Arrows point to left bundle branch.

occur without Mahaim fibers bypassing part of the node. This would seem to indicate that either AV node bypass is not the mechanism of production of the WPW syndrome, or that there are two anatomic substrates producing a similar electrocardiographic abnormality—one with and one without accessory communications.

In cases in which no accessory communications or Mahaim fibers proximal to part of the AV node are found, the concept of accelerated conduction is an inviting hypothesis. The inflammatory changes about the node in case 2 coupled with the elastosis of part of the node might support the concept of accelerated conduction through the node and conduction system. Inflammatory changes in this region were also found in the first case and in previously reported cases of the WPW syndrome. It would thus appear that there are at least eight cases with inflammatory changes in the conduction system.

It must be stressed, however, that with the present two cases there are now only four cases in the literature, studied by two observers, in which all possible atrioventricular communications were studied. In three, accessory communications outside the conduction system have been found. Furthermore, since every tenth section was studied in the left atrioventricular ring in our present two cases, the certainty of the presence or absence of atrioventricular communications on the left side is not so complete as that on the right side, where complete serial sections were studied. Many more anatomic studies of this type by varied observers are necessary to establish an anatomic base for this electrocardiographic abnormality.

As concerns the pathologic changes in the heart in general, in our cases we are dealing with Chagas' myocarditis in case 1.[24-27] In case 2, we may be dealing with the granulomatous type of Chagas' myocarditis, but since complement fixation tests were not done and the Leishmania were not found in the myocardium, this is uncertain. The characteristics of the myocarditis conform in general with what has been described in the literature for an unusual type of Chagas' myocarditis.[27] The involvement of the conduction system in Chagas' disease is well known.[27] It is questioned, however, whether there is a specific predilection for the conduction system.[28]

An additional point of interest is the ab-

normal course and the complete destruction of the right bundle branch in case 2, which corresponded with the electrocardiographic pattern of complete right bundle-branch block. It may be theorized that this was hemodynamically produced by the congenital pulmonic insufficiency. Such hemodynamic genesis of complete left bundle-branch block has been previously postulated by Lev.[29] An added detail is the well-preserved right bundle branch distal to the point of obstruction. As is well known, obstruction at any point in the conduction system does not result in the disappearance of the structures distal to this point, since the integrity of individual structures are related to the blood supply of these structures as in any other part of the myocardium. Complete right bundle-branch block is common in Chagas disease.[28] The association of the WPW syndrome with bundle-branch block has recently been discussed by Pick and Fisch.[30]

Summary

The atrioventricular communications and the AV node, bundle, and bundle branches of two cases with the WPW syndrome were studied histologically. One case was that of chronic Chagas' myocarditis and the other possible chronic Chagas' myocarditis.

Accessory muscular communications in the right atrioventricular junction were found in one heart, and no communications outside the conduction system in the other.

Inflammatory changes were found in the conduction system of both hearts.

The literature of the anatomic changes in hearts with the WPW syndrome, and that with the presence of accessory atrioventricular muscular communications without the WPW syndrome are reviewed.

From the study of the literature and of our two cases, it appears that some cases of the WPW syndrome are associated with accessory communications and others are not, and accessory communications may be present without this syndrome. Of the four cases with this syndrome, however, in which a thorough study has been made of all possible conduction pathways, three showed accessory communications. On the other hand, inflammatory changes in the pre-atrioventricular nodal area, AV node, bundle and bundle branches have been found in many cases of the WPW syndrome.

It is thus clear that an anatomic base has as yet not been established for the WPW syndrome. It is possible that a different mechanism may be responsible in different cases. The high incidence of inflammation of the conduction system in the studied cases makes accelerated conduction an attractive hypothesis, where no accessory bundles have been found. More correlative histologic and clinical work needs to be performed in this field.

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Leopold Auenbrugger
1722—1809

Convinced by personal experience, I contend that the sign about which this book treats is of the utmost importance, not only for the diagnosis, but also for the treatment of diseases, so that it ranks in value immediately after the examination of the pulse and the breathing. I contend that an abnormal tone in the thorax is, in every disease, a certain sign of the existence of serious danger. (Quoted from the English translation of 1824, by John Forbes, M.D.)

Treatment of Complete Transposition of the Great Vessels with the Blalock-Hanlon Operation

By JOHN L. OCHSNER, M.D., DENTON A. COOLEY, M.D., LEONARD C. HARRIS, M.D., AND DAN G. MCNAMARA, M.D.

TRANSPOSITION of the great vessels is not a rare anomaly. It accounts for 8 per cent and is the fourth most common of all congenital heart diseases, being surpassed in frequency only by patent ductus arteriosus, ventricular septal defect, and tetralogy of Fallot.[1] Furthermore, transposition is a notorious first cause of death from congenital heart disease in childhood. At the Texas Children's Hospital transposition of the great vessels is the most frequent congenital heart malformation found at autopsy, accounting for 64 (21 per cent) of the 300 deaths from congenital heart disease.

The high mortality from transposition of the great vessels is not usually due to a delay in diagnosis, since the most prominent symptoms, cyanosis, dyspnea, and growth failure usually cause the parents to seek medical help early. Nor is it due to difficulty in diagnosis, which according to Taussig[2] can usually be made clinically with the help of an electrocardiogram and a roentgenogram, although confirmation by angiocardiogram is often desirable. The prognosis of this disease is so grave that the great majority of cases do not survive beyond the first year of life and only the occasional case survives to adolescence or adult life. Blalock and Hanlon[3] found an average life expectancy of 19 months in 123 cases, and if one excludes six of their patients who lived 10 years or longer, the average duration of life was only 5½ months. Keith and co-workers[4] reported that 52 per cent of infants with transposition of the great vessels were dead at 1 month and 86 per cent dead at 6 months, the average length of survival being only 3 months.

The frequency and poor prognosis of this condition have stimulated the surgical development of many palliative and some corrective procedures, but in general the unsatisfactory results have discouraged most clinicians.[5–15] The purpose of this paper is to present our experience in the management of patients with complete transposition of the great vessels and to report the results of palliative surgery for this disease by the creation of an atrial septal defect by the use of the Blalock-Hanlon technic.

Since success of the various palliative and attempted corrective procedures depends on some alteration of the hemodynamics, it is pertinent to review briefly the physiology of this condition.[16–18] In utero the origin of the aorta from the right ventricle causes little physiologic disturbance, since the right ventricle serves as a systemic ventricle during fetal life. After birth, in the absence of a shunt between the right and left sides of the heart, two separate circulations exist (fig. 1). Unsaturated systemic venous blood returns to the right atrium and enters the right ventricle and transposed aorta. Saturated blood returns from the lung to the left atrium and recirculates through the pulmonary system via the transposed pulmonary artery. Obviously life cannot be sustained if there is no interchange of blood between these two independent circuits. A shunt, resulting in partial saturation of the systemic blood, must be present for survival; to prevent overloading of the pulmonary or systemic circulations the shunt must be in two directions. The shunt may be bidirectional at one site or in opposite directions at two or more sites. Shunts may

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Supported in part by the U. S. Public Health Service under grants H-3137 and HTS-5387, the Houston Heart Association, and the Wharton County Heart Association through the Texas Heart Association Research Committee.

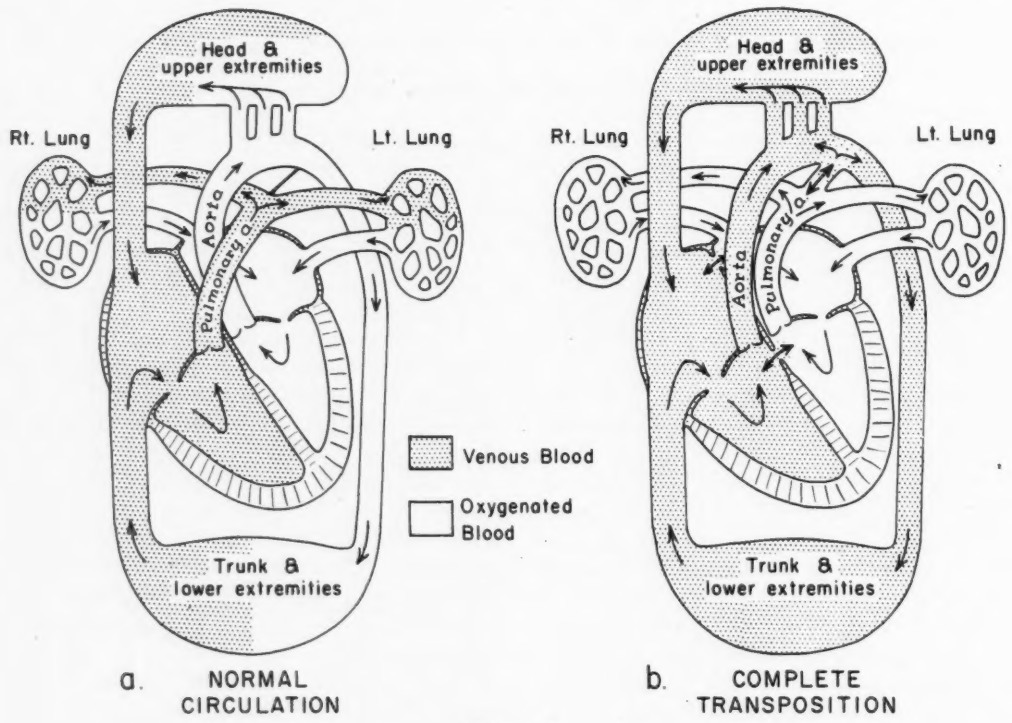

Figure 1

Drawing showing comparison of normal circulation in (a) and circulation in complete transposition of the great vessels in (b). Mixing of oxygenated and unoxygenated blood in complete transposition may occur at a patent ductus arteriosus, ventricular septal defect, or patent foramen ovale.

be present as a ventricular septal defect, patent foramen ovale, and patent ductus arteriosus, and various combinations may be demonstrated at cardiac catheterization.[17]

Among 64 cases of transposition of the great vessels autopsied at the Texas Children's Hospital from 1956 to 1960, the most common site of a shunt was through a ventricular septal defect (table 1). Although a patent foramen ovale was present in 25 cases, a true atrial septal defect was encountered only six times. This is significant, since the valvular nature of a patent foramen ovale tends to prevent free bidirectional shunting of blood, and left-to-right shunting of blood is usually retarded. A patent ductus arteriosus, though often present in infants with transposition, does not increase the chance of survival.[1] The inadequacy of a patent ductus arteriosus or foramen ovale to provide adequate shunting of blood was evident in 10 of our autopsied newborn infants who had only these associated defects. Rare sites of shunting in our series included anomalous venous return from the lungs and aorticopulmonary septal defect (table 1). Dilated bronchial arteries may carry unsaturated blood to the left side of the heart for oxygenation. Communications have been described between the right internal jugular vein and left atrium and between the azygos vein and left atrium, permitting systemic venous blood to be oxygenated by passing through the pulmonary circulation.

The severity of symptoms in a given case is determined by the degree of anoxemia and congestive heart failure. The degree of anox-

emia is firstly dependent on the adequacy of the intracardiac shunt, usually through either a ventricular septal defect, atrial communication, or both. Secondly, it is dependent on the degree of pulmonary vascular resistance. Although pulmonary stenosis was described in more than one third of the cases reported by Becker and Brill,[19] Edwards[16] found it to be uncommon. In our autopsy series pulmonary stenosis occurred in six instances, or 9 per cent of the 64 cases of transposition of the great vessels. A mild-to-moderate pulmonary stenosis or increased pulmonary arteriolar resistance in the presence of an adequate left-to-right shunt tends to improve mixing and thereby increase longevity.

During the past 6 years surgical treatment of the critically ill infant admitted to our hospital with complete transposition of the great vessels consisted in most instances of creation of an interatrial septal defect with use of a modified Blalock-Hanlon technic.

Table 1

Associated Congenital Defects in 64 Autopsied Cases of Transpositon of Great Vessels

Defect	Number	
Ventricular septal defect	43	
Isolated ventricular septal defect		20
Single ventricle		18
Taussig-Bing anomaly		5
Patent ductus arteriosus	31	
Patent foramen ovale	25	
Atrial septal defect	6	
Coaretation of aorta	7	
Pulmonary stenosis	6	
Aortic arch atresia and hypoplasia	5	
Pulmonary atresia	4	
Mitral atresia	3	
Tricuspid atresia	3	
Anomalous pulmonary venous return	2	
Aorticopulmonary septal defect	1	
Total	136	

Operative Technic

The anesthetized patient is placed in the left lateral position and a right lateral incision is made through the fifth intercostal space (fig. 2). The lung is retracted and the pericardium is entered anterior and parallel to the course of the right phrenic nerve. Confirmation of the diagnosis may be made by aspirating blood from the aorta and right pulmonary artery and demonstrating blood of higher oxygen content in the pulmonary artery than the aorta. The two major pulmonary veins to the right lung are dissected inside the pericardium and encircled with heavy silk ligatures for traction and temporary occlusion. The right main pulmonary artery is also encircled with a heavy ligature. During the period of temporary occlusion of the pulmonary veins the pulmonary artery must be occluded to prevent engorgement of the lung and development of hemorrhagic edema. A curved vascular clamp is placed across the base of the pulmonary veins at the junction with the left atrium (fig. 2). The pulmonary artery and veins are first occluded with the ligatures. The vascular clamp is closed incorporating a portion of the right atrium. Two incisions are made in the heart, one entering the right atrium anteriorly and the other entering the left atrium posteriorly. The tissue between these incisions, which is attached to the atrial septum, is then grasped with a hemostatic forceps. As the arterial clamp is partially released, the septum is withdrawn and trimmed progressively, a fragment being excised approximately 2 cm. in diameter (fig. 2). Usually the fossa ovalis is pulled into view medially during this maneuver. After the septal fragment is excised, the septum retracts back inside the heart. The two margins of incision are approximated with a continuous 5-0 black silk suture and the occluding ligatures on the pulmonary artery and veins are removed. Usually the period of venous occlusion is brief, being between 6 and 8 minutes, and therefore pulmonary congestion does not occur. The patient's color and general condition improve immediately. The pericardium is closed loosely. The thoracotomy incision is repaired and intercostal underwater seal drainage is used for 24 hours.

Clinical Material

Over the past 6 years 45 patients with transposition of the great vessels underwent operation for the creation of an atrial septal

Table 2

Distribution of Age Among Patients Undergoing Creation of Atrial Septal Defect for Transposition of Great Vessels

Age	Number	Percentage
0-1 year	33	73
0-3 months	22	49
3-6 months	5	11
6-9 months	4	9
9-12 months	2	4
1-2 years	5	11
2 + years	7	16
Total	45	100

defect by the Blalock-Hanlon technic. There were 33 males and 12 females, a male predominance of 2.75 to 1. A wide variation in age distribution was noted, the youngest child being 26 hours old and the oldest 9 years. The majority of the children, however, were operated upon during the first year of life (table 2). Twenty-two (49 per cent) were less than 3 months of age at the time of surgery.

The prime criterion for selection of a patient for surgical treatment was severe anoxemia. The additional complication of congestive heart failure was not considered a contraindication for operation on the assumption that cardiac failure was accompanied by anoxemia. One patient operated upon at 2 months of age with severe anoxemia and congestive heart failure was still improved 1½ years later. Cases of transposition of the great vessels associated with single ventricle, pulmonary atresia, mitral atresia, or tricuspid atresia were not included in this study because these cases have different hemodynamics, functioning as a single ventricle.

Results

The over-all survival rate of 45 patients in whom the creation of an atrial septal defect by the Blalock-Hanlon technic was performed was 67 per cent (table 3). Fifteen (33 per cent) of the 45 cases in this study have died since operation. Thirteen (29 per cent) succumbed in the immediate postoperative period, whereas two died after discharge from the hospital, having survived for periods of 2 months and 9 months, respectively. During

Table 3

Results of Operation (Creation of Atrial Septal Defect) in Transposition of the Great Vessels

Year	Number of operations	Survivals	Percent survivals
1954–1957	17	7	41
1958–1960	28	23	82
Total	45	30	67

the first 3 years of this study only 9 of 17 patients (53 per cent) survived the early postoperative period and two more subsequently died, the mortality rate for this group being 59 per cent. In contrast there were only five deaths in the 28 patients operated upon during the last 3 years (a mortality rate of 18 per cent). One of these five patients died 7 days after surgery without an autopsy but was known to have a birth injury with a fractured skull.

Blood and ear oxygen saturations were determined before and after surgery in 13 cases (table 4). All except two showed a significant improvement in saturation and the average increase in the 13 cases was 17.5 per cent. Four of the cases who had preoperative determinations of oxygen saturation died after surgery. Only two of the four showed a rise in oxygen saturation of more than 10 percentage points, and one of these, who was improved by surgery died 8 months afterwards from a cerebral hemorrhage.

The majority of patients had significant and often striking symptomatic improvement following creation of the atrial septal defect. They have shown a decrease in cyanosis and an increase in exercise tolerance. A few were able to live an almost normal life, engaging in most activities enjoyed by other children of equal age.

Discussion

Complete correction of transposition of the great vessels is obviously the ideal treatment and continues to provide a challenging technical and physiologic problem. Surgical correction could be achieved either by transposing the aorta and pulmonary artery or by converting the systemic and pulmonary veins to conform with the arterial transposition.

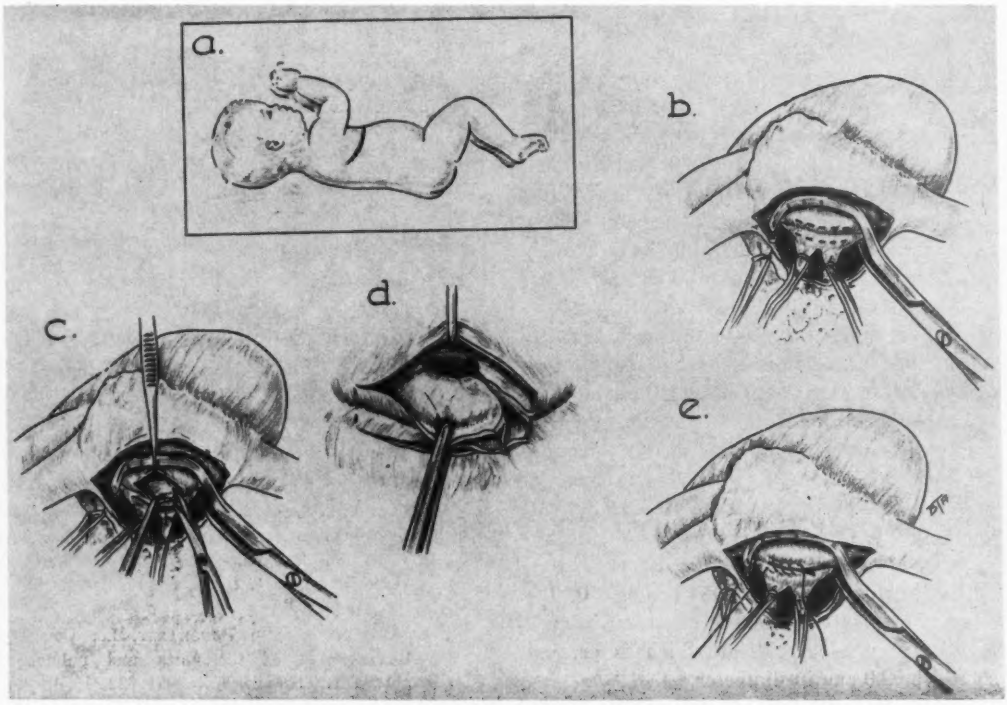

Figure 2

Drawing showing technic of creation of interatrial septal defect in treatment of complete transposition of great vessels. In (a) an incision is made in the right fifth intercostal space. In (b) a curved clamp is placed across base of the right pulmonary veins and right atrium. Dotted lines show position of incisions into right and left atria. In (c) and (d) portion of atrial septum is withdrawn from the heart as the clamp is partially released. Fossa ovalis is visible at apex of septal specimen. In (e) the atrial incision is closed with a continuous fine silk suture.

The latter method has a distinct advantage in eliminating the necessity of transposing the coronary blood supply, which is derived from the aortic annulus at its origin from the right ventricle. Experimental and clinical efforts toward complete correction of this anomaly in our hospital were directed toward atrial repositioning, excising the interatrial septum and replacing the septum with a spiraled cloth prosthesis. Results with this technic were not satisfactory. Recently Senning[15] reported a unique and ingenious method of transposing the two atria during cardiopulmonary bypass. He reported one clinical success with this method, and Kirklin and associates[20] have recently had four patients survive this operation among 11 attempted total corrections. Unfortunately, the complicated nature of a totally corrective operation may limit the usefulness of this procedure in the gravely ill newborn infant.

Since most of the patients with this malformation die before 6 months of age, and because of the technical difficulties and detrimental physiologic alterations associated with open-heart surgery in infants of this age, a palliative surgical procedure of less magnitude seems desirable. On the basis of our recent experience with 82 per cent survival in patients in whom an adequate atrial septal defect was created, this palliative treatment of complete transposition of the great vessels appears to

be satisfactory. At the same time, the presence of an atrial septal defect will not hinder an intraatrial complete repair at a later date when the patient reaches a more optimum size and general physical state for radical repair.

Certain recommendations for management of these cases seem justified at this time. Creation of an interatrial septal defect by the Blalock-Hanlon technic should be employed in all severely anoxemic infants with complete transposition of the great vessels. Angiocardiography done in the lateral position is a useful method of demonstrating the absence of an adequate interatrial communication. Lack of early opacification of the left atrium provides the indication for creation of an adequate interatrial communication. The larger the atrial defect produced the more efficient will be the mixing of the unoxygenated and oxygenated blood. The size of the defect created will naturally be limited by the size of the heart; however, even in an infant less than 3 months of age the defect which is created should be 2.0 cm. in diameter.

Summary

Transposition of the great vessels is the most frequent cause of death from congenital heart disease in childhood. The high incidence and poor prognosis of this condition have stimulated the development of many palliative and corrective surgical procedures, but in general their results have been discouraging.

During the past 6 years at the Texas Children's Hospital 45 patients with transposition of the great vessels have undergone palliative operation by the creation of an atrial septal defect, using the Blalock-Hanlon technic. The prime criterion for the selection of a patient for surgical treatment was severe anoxemia with or without associated congestive heart failure. The majority of cases were under 1 year of age and 49 per cent less than 3 months of age at the time of surgery.

Among 28 patients operated upon during the past 2 years 23, or 82 per cent, survived operation with general improvement. Use of this palliative operation is recommended for the small infant or critically ill patient, and totally corrective procedures should be reserved until conditions are more favorable for survival.

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TENTH OBSERVATION

Of Scirrhus of the Lungs, and its Symptoms

XXXVIII. By scirrhus of the lungs I mean the degeneration of the natural spongy substance of the organ into an indolent, fleshy mass.

A portion of sound lung swims in water, but this carniform degeneration sinks. There is often observed a vast difference in the character of these scirrhi, in respect of hardness, color, and component parts. Thus in inflammatory diseases of the chest proving fatal on the fifth, seventh, or ninth day, the lung is very often found so completely gorged with blood as to resemble liver in every respect, both as to colour and consistence. . . .

XXXIX. The presence of scirrhus of the lungs, in its primary, unsoftened condition, may be suspected from the following signs:

Together with diminution or entire loss of the natural sound over the affected part, there is an infrequent cough without any expectoration, or with only a scanty excretion of viscid and crude sputa. During a state of quiescence there is nothing to be observed much amiss, either in the condition of the pulse or respiration; but upon any considerable bodily exertion, or after speaking for some time, these persons become speedily exhausted, anxious, and breathless, and complain of a sense of dryness and roughness in the throat. All the above symptoms are more severe in proportion as the scirrhus is more extensive.—From *On Percussion of the Chest.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 136.

Comparative Effects of Thyroxin Analogues as Hypocholesteremic Agents

By MAURICE M. BEST, M.D., AND CHARLES H. DUNCAN, M.D.

DRIED THYROID SUBSTANCE or the pure natural hormones, L-thyroxin and L-triiodothyronine, effect a reduction in the serum total cholesterol of euthyroid individuals when administered in sufficient amount.[1-3] Their general clinical use to reduce elevated serum cholesterol levels in the hope of favorably influencing the course of atherosclerosis has been limited by two factors. When given in moderate dosage, dried thyroid substance effected a prompt reduction in serum cholesterol, but despite continuation of the hormone the reduction was not sustained.[4] This "escape" is presumed to be due to suppression of thyrotropin secretion by the administered thyroid and consequent decrease in production of endogenous thyroid hormone. When the dose of administered hormone is increased to maintain a reduced serum cholesterol level, hypermetabolism manifested by an increased basal metabolic rate, tachycardia, and weight loss may occur. An ominous consequence of thyroid hormone administration to patients with coronary artery disease is the frequent increase in severity of angina pectoris.[5]

If some modification of the chemical structure of L-thyroxin or L-triiodothyronine resulted in an analogue that largely retained the effect of the natural hormones on cholesterol metabolism but was sufficiently less active in its other metabolic effects, a way out of this dilemma would be available.

In the rat the formic acid analogue of thyroxin, tetraiodothyroformic acid, has been shown to exert an effect on cholesterol metabolism that is disproportionate to its effect on oxygen consumption, growth, and thiouracil-induced goiter.[6-8] More recent studies in the rat of a series of thyroxin analogues have shown that the D-isomers of thyroxin and triiodothyronine also exert a disproportionate effect on cholesterol metabolism.[9]

In view of these observations in the experimental animal that replacement of the L-alanine side chain of the natural thyroid hormones with either a carboxyl group or D-alanine resulted in analogues displaying a degree of dissociation of effects, these analogues were compared with L-thyroxin as hypocholesteremic agents in the euthyroid human subject. To study further the general metabolic effects of these analogues their ability to serve as thyroid replacement therapy in human myxedema was also determined.

Material and Methods

Seventeen euthyroid patients were observed for periods up to 4 years. Ten were male and seven female; ages ranged from 28 to 77, with a mean of 56 years. Three had elevated serum cholesterol levels without evidence of cardiovascular disease (patients 1, 2, and 3). The remaining 14 patients had arteriosclerotic heart disease; 12 had had myocardial infarction 3 or more months prior to study (patients 4 to 15), four had moderate to severe angina pectoris (patients 13 to 16), and three had congestive heart failure controlled by digitalis (patients 4, 5, and 17). Serum protein-bound iodine levels of the patients ranged from 4.7 to 6.9 μg. per 100 ml.

Mean serum cholesterol levels of the individual patients before treatment ranged from 244 to 394 mg. per 100 ml., the mean for the group being 286. Patients with wide fluctuations in serum cholesterol, such as occur in idiopathic hyperlipemia, and patients with overt diabetes mellitus were excluded. Major criteria for inclusion were the ability and willingness of the subjects to cooperate in the study as demonstrated during the initial control period. Six patients were hospitalized throughout the period of study

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Supported by research grant H-1946 from the National Heart Institute, U. S. Public Health Service, and the Kentucky Heart Association.

Presented at the meeting of the Council on Arteriosclerosis, The American Heart Association, St. Louis, Missouri, October 21, 1960.

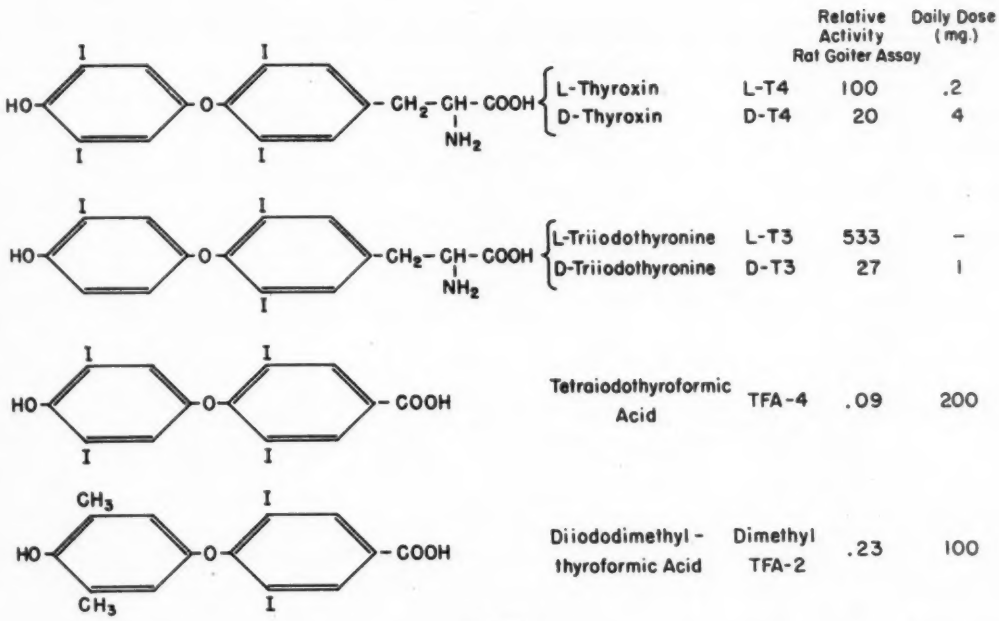

Figure 1

Thyroid hormones and analogues studied in the human subject. The goiter-inhibiting activities, with L-*thyroxin assigned a value of 100, are those determined in our laboratory. The daily dose is that given the euthyroid patients.*

and consumed a fairly constant diet; the remaining patients were seen as outpatients and continued their usual diets.

All patients were seen at 2- or 3-week intervals, the visits being scheduled at approximately the same time of day. After a 20-minute rest period the pulse rate and body weight were recorded, blood was drawn, and the clinical state of the patient was evaluated. Serum total cholesterol was determined by the method of Abell et al.[10]

The L-thyroxin and analogues were given orally, in single or twice daily doses. The total daily dose of each hormone is indicated in figure 1. During the periods immediately preceding and following those of drug administration the patients received placebos that were identical in appearance to the active drug. Whenever a change in the appearance of the medication or the frequency of administration was necessitated by the form available, it was accomplished during the placebo period.

Thirty-four treatment periods of 6 weeks to 10 months were completed in the 17 patients, each being preceded and followed by a period of placebo administration. Five patients received only one drug, the other patients two to four.

Seven myxedematous patients were also observed for periods ranging up to 5 years. Six were female and one male; ages ranged from 37 to 74 years, with a mean of 55 years. In three the etiology of the myxedema was unknown; in the remaining four it was the result of thyroid surgery or therapeutic radioiodine. Prior to treatment basal metabolic rates ranged from minus 39 to minus 18 per cent, serum protein-bound iodine from 0.5 to 1.7 μg. per 100 ml., and serum total cholesterol from 260 to 450 mg. per 100 ml.

After the diagnosis of myxedema was established and replacement therapy was instituted with L-thyroxin or L-triiodothyronine, the patients were observed as described for the euthyroid subjects. In addition, special attention was directed to the clinical evidences of the thyroid status, and determinations of the basal metabolic rate were made at frequent intervals in the four patients in whom the results were most reproducible. Each of the analogues under study was then substituted for the natural hormone in three to seven of the patients for periods of 6 to 12 months each. The doses employed ranged from one-half to one and one-half those employed in the euthyroid subjects, and were adjusted in accordance with the individual responses of the patients.

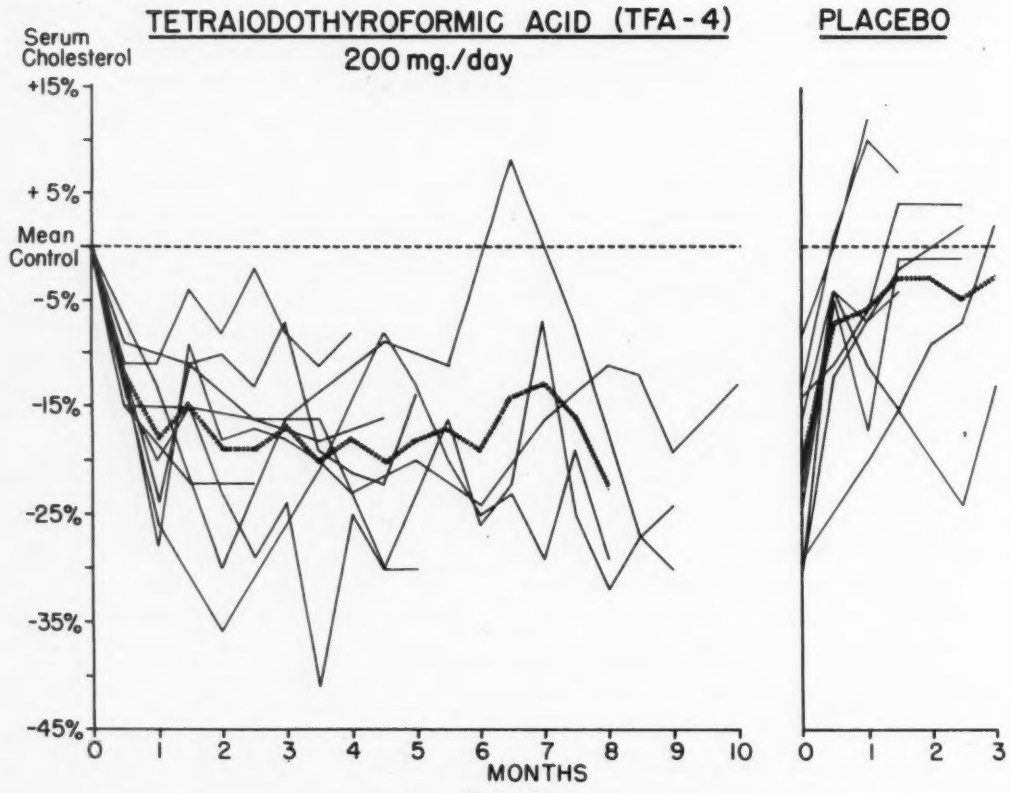

Figure 2

The mean control serum cholesterol (broken line) of patients receiving TFA-4 was 287 mg. per 100 ml. Changes in the serum cholesterol of each patient (solid lines) are expressed as percent deviation from individual control levels. The mean change in serum cholesterol for all patients during drug and the immediately following placebo periods is shown by the heavy line. Patients 4 to 9, 12, 13, and 17.

Results

Nine of the 17 euthyroid patients received tetraiodothyroformic acid (TFA-4) for periods of 2½ to 10 months of continuous administration (fig. 2). In all patients there was a reduction in the mean serum cholesterol during the treatment period. For the group the mean control serum cholesterol level was 287 mg. per 100 ml.; the mean treatment level was 235, a mean reduction of 52 mg. per 100 ml. or 18 per cent of the control level. When a placebo was substituted for the TFA-4, there was a prompt return to the pretreatment range of serum cholesterol.

Dimethyldiiodothyroformic acid (dimethyl-TFA-2), which in the rat was found to have a disproportionate effect on cholesterol metabolism comparable to that of TFA-4 and to possess twice the activity of the latter analogue (fig. 1), was given to six patients. Due to the limited supply the periods of administration were only 1½ to 4 months. The effect on serum cholesterol (fig. 3) was very similar to that of TFA-4; with the substitution of a placebo there was again a prompt return to the pretreatment range.

To date the studies of the effect of D-thyroxin (D-T4) have been completed in only four of the 17 patients (fig. 4). The mean control serum cholesterol level of these patients

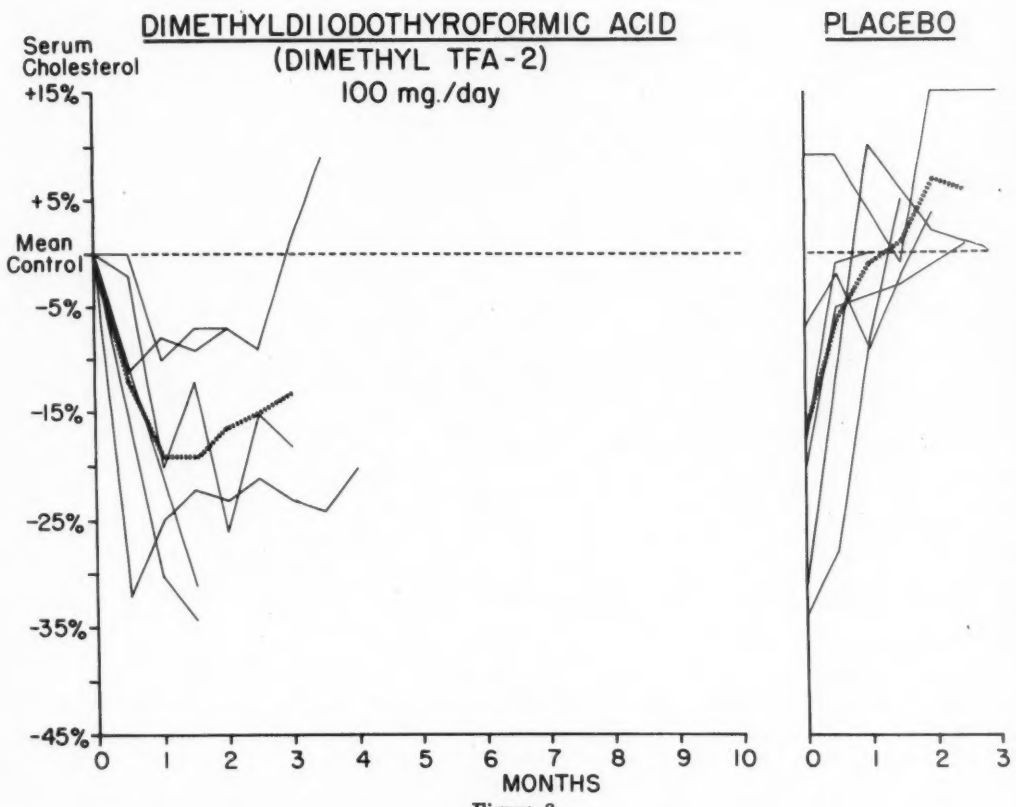

Figure 3

The mean control serum cholesterol of patients receiving dimethyl-TFA-2 was 284 mg. per 100 ml. Responses to drug and placebo administration are indicated as in figure 2. Patients 5 to 7, 11, 13, and 16.

was 294 mg. per 100 ml., the mean level during the 4- to 8-month treatment period was 219, a reduction of 26 per cent. Again the serum cholesterol returned to the pretreatment range following the substitution of a placebo.

Eight patients received D-triiodothyronine (D-T3) for periods of 3 to 10 months (fig. 5). The administration of 0.5 mg. of D-T3 twice daily resulted in a fall in mean serum cholesterol from 294 to 225 mg. per 100 ml., the reduction in the individual patients ranging from 42 to 94 mg. per 100 ml. In the six patients in whom a placebo had been substituted for the D-T3 at the time of this report, a return of the serum cholesterol to the control range occurred within 6 weeks.

The mean control serum cholesterol of the seven patients receiving L-thyroxin (L-T4) was 312 mg. per 100 ml. (fig. 6). Although the response of the individual patients was somewhat more variable than that to the analogues, the mean reduction of 15 per cent of the control level is not appreciably different from that resulting from the formic acid analogues (fig. 7). No tendency to escape from this effect was observed during the mean treatment period of 7½ months; substitution of placebo again resulted in a prompt return to the pretreatment range.

Undesirable side effects occurred in several of the patients while they were receiving the formic acid analogues. Diarrhea and cramping abdominal pain were experienced by two

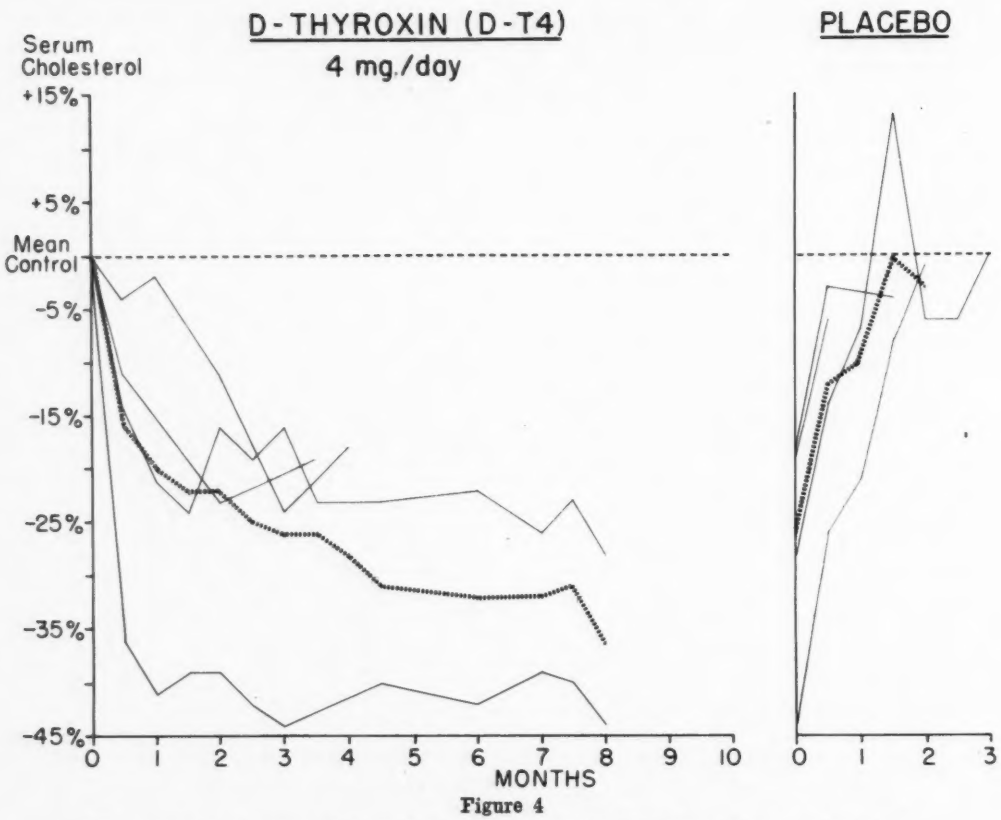

Figure 4

The mean control serum cholesterol of patients receiving D-T4 was 294 mg. per 100 ml. Responses to drug and placebo administration are indicated as in figure 2. Patients 6, 13, 14, and 17.

patients during the administration of TFA-4 and by the same two patients during the administration of dimethyl-TFA-2. Another patient developed an extensive acneiform eruption and a fourth patient had salivary gland swelling during TFA-4 administration, both reactions being typical of iodism. In three of these four patients the side effects were sufficiently severe to necessitate discontinuation of the medication; all subsided when a placebo was substituted. No toxic effects on liver, kidney, or bone marrow were observed with any of the analogues.

None of the hormones at the dose employed had an appreciable effect on body weight. Mean resting pulse rate was 6 per minute higher during the period of L-T4 administration than during the control period; no increase in mean resting pulse resulted from the analogues. Increase of angina pectoris occurred in two patients during the study, in both instances during L-T4 administration.

In the myxedematous patients a clinically euthyroid state was maintained by each of the analogues when given in appropriate dosage. The mean daily amount of each compound required to achieve this result was as follows: L-T4, 0.3 mg.; L-T3, 0.075 mg.; D-T4, 4 mg.; D-T3, 0.75 mg.; dimethyl-TFA-2, 100 mg.; and TFA-4, 220 mg. That all the analogues studied are calorigenic when given in adequate amount is indicated by the basal metabolic response of one patient who was hospitalized throughout the 5-year period of study

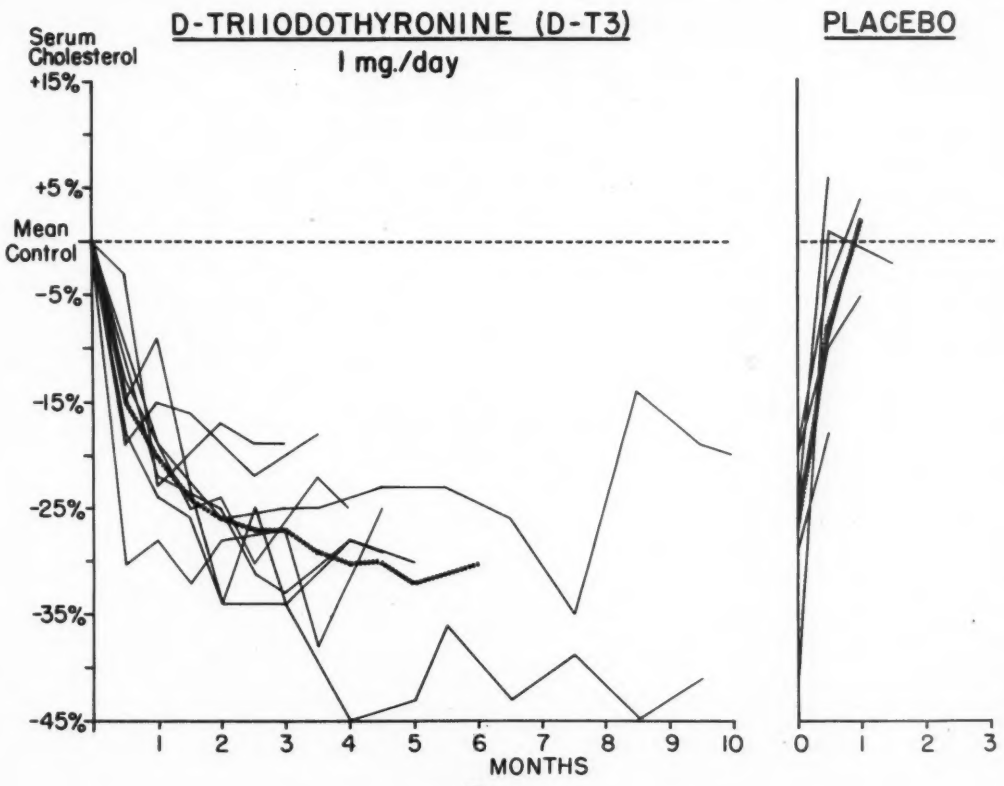

Figure 5

The mean control serum cholesterol of patients receiving D-T3 was 294 mg. per 100 ml. Responses to drug and placebo administration are indicated as in figure 2. Patients 1, 3, 4, 7, 9 to 11, and 15.

(fig. 8). Each analogue was tolerated by the patients with myxedema without the development of angina or other undesirable effects in doses equal to or exceeding those employed in the euthyroid subjects.

Discussion

Each of the four analogues studied, TFA-4, dimethyl-TFA-2, D-T4, and D-T3, resulted in a mean reduction of serum total cholesterol of the euthyroid patients. Although the subjects displayed the usual variability in serum cholesterol during both control and treatment periods, the consistency with which the mean level during treatment was reduced and the return to the pretreatment range when a placebo was substituted would seem to eliminate the possibility that these changes in serum cholesterol levels were due to spontaneous fluctuation.

The limited supply of dimethyl-TFA-2 prevented a sufficiently long period of administration to determine if its hypocholesteremic effect would be sustained. With the other analogues, no tendency of serum cholesterol to return toward control levels during continued administration for 6 to 10 months was observed. The "escape" from the initial hypocholesteremic effect of dried thyroid observed by Strisower et al.[4] was evident by 6 weeks and essentialy complete by 24 weeks. Thus it seems likely that if escape were to occur with these analogues it would have been observed during the present study. In the case of D-T4,

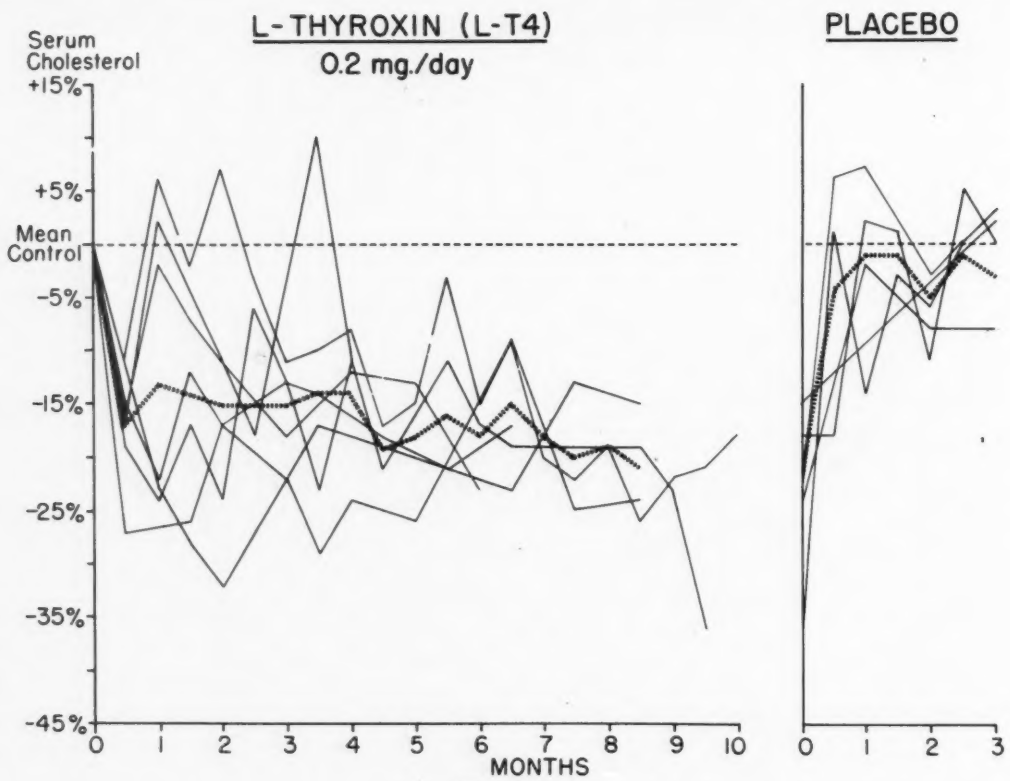

Figure 6

The mean control serum cholesterol of patients receiving L-T4 was 312 mg. per 100 ml. Responses to drug and placebo administration are indicated as in figure 2. Patients 1 to 3, 5, 13, 14, and 17.

the maintenance of reduced serum cholesterol levels throughout the period of its administration to euthyroid subjects has been noted by Starr et al.[11] and by Jones.[12] In view of the presumed mechanism of this escape phenomenon, its failure to occur with these analogues may be due to their relatively lesser inhibition of thyrotropin secretion.[9]

The analogues, unlike L-T4, did not induce or aggravate symptoms in any of the 14 patients with arteriosclerotic heart disease. None developed or experienced intensificaton of angina pectoris or congestive heart failure during therapy with the analogues. One patient did have a recurrent myocardial infarction during the placebo period after treatment. Boyd and Oliver[13] also observed no intensification of angina with a 10-mg. daily dose of D-T4, but unlike our experience they did observe an increase in angina with D-T3 at a daily dose of 1 mg. It is noteworthy that in their study about one half of the patients who experienced intensification of angina pectoris during administration of various thyromimetic compounds displayed no concomitant increase in basal metabolic rate.

Attempts early in our study to evaluate any possible effects of the analogues on basal metabolic rate of the euthyroid patients were abandoned, the variability of repeated determinations, even in the hospitalized patients, being sufficient to obscure any moderate change. The lack of effect of the analogues on resting pulse rate and body weight suggests that they

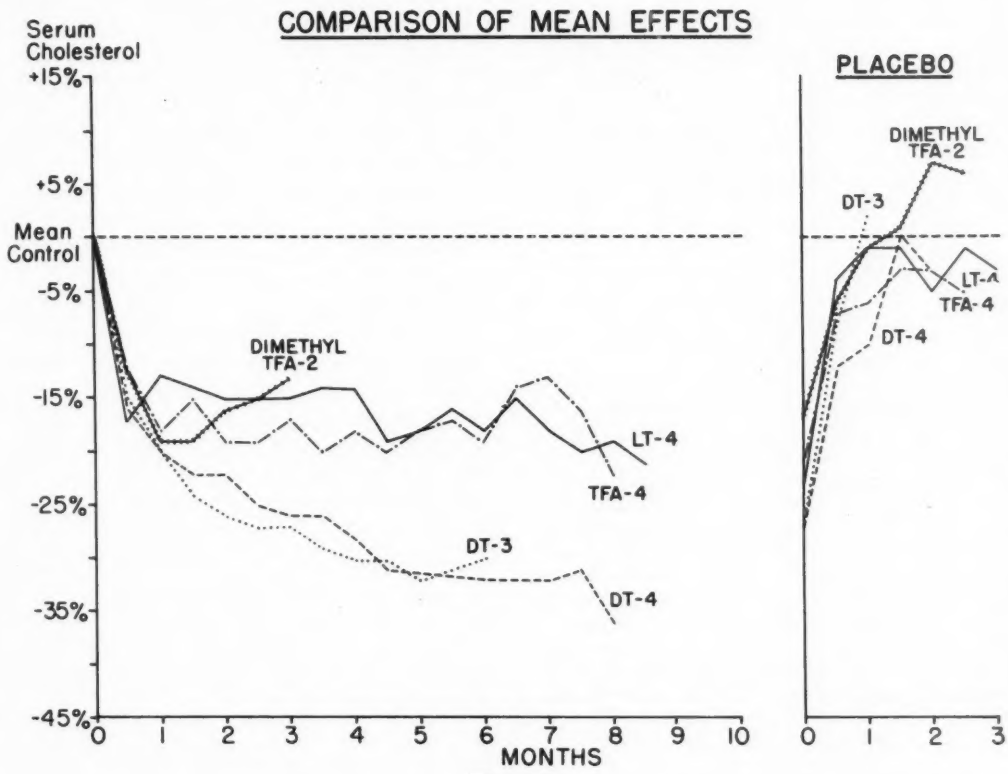

Figure 7

To facilitate comparison, the mean responses of serum cholesterol to L-T4 and the several analogues are shown.

did not cause any very pronounced hypermetabolism.

It should not be inferred that any of these analogues are without calorigenic activity, since such activity was clearly demonstrated in the myxedematous patients. It would appear, however, that the dissociation of cholesterol-lowering and calorigenic effects, though by no means complete, was of such a degree as to permit a dose that will predictably lower serum cholesterol without undesirable complications in the majority of patients with arteriosclerotic heart disease.

L-thyroxin was included in the study with the expectation of observing effects essentially similar to those reported with moderate doses of dried thyroid, that is an initial hypocholesteremic effect with subsequent tendency to escape. These expectations were only partially realized; serum cholesterol did fall moderately in the early weeks but the anticipated escape did not occur, the reduced level being maintained throughout the period of hormone administration, which was 6 or more months in all but one of the patients. Confirmation of this apparent difference in the effects of dried thyroid and L-thyroxin needs further study with comparable doses of the two materials.

At the doses employed, the hypocholesteremic effect of the L-T4 was less than that of the D-T4 and D-T3. The mean increase in pulse rate suggests that the L-T4 at this dose did have some calorigenic effect, and both patients in this group who had angina pectoris experienced an increase in symptoms.

The high dosage of TFA-4 and dimethyl-

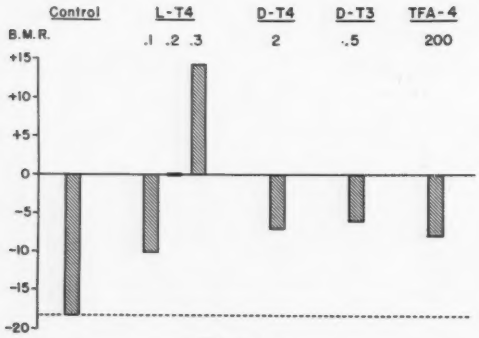

Figure 8

Response of the basal metabolic rate to L-T4 and three of the analogues in a 35-year-old patient with myxedema induced by I^{131} for alleviation of congestive heart failure due to mitral insufficiency. Each hormone was given for a minimum period of 6 months. Basal metabolic rates indicated are the means of determinations made at approximately monthly intervals. Congestive failure was well controlled throughout the period except during the administration of L-T4, 0.3 mg. daily. As in all the myxedematous subjects, the serum cholesterol was more responsive to the thyroid hormones than in the euthyroid subjects; initial pretreatment control was 302 mg. per 100 ml., mean levels during periods of replacement therapy ranged from 155 to 220 mg. per 100 ml.

TFA-2 necessitated by their low activity probably precludes their general use because of the hazard of iodism in the sensitive individual. This limitation does not apply, however, to D-T3 and D-T4, which are effective in daily amounts of 1 to 4 mg.

A possible explanation for the disproportionate effect of these dextro isomers of thyroxin and triiodothyronine on cholesterol metabolism is offered by the recent observation of differences in their tissue distribution as compared to the L-isomers. The D-isomers were found in a relatively higher concentration in the liver than in skeletal and cardiac muscle as compared to the natural hormones.[14, 15] In view of the dominant role of the liver in the regulation of plasma cholesterol, the disproportionate effect on serum cholesterol of the D-isomers may be attributable to their relatively higher concentration in this organ.

Summary

L-thyroxin and four thyroxin analogues were administered to a group of hypercholesteremic euthyroid patients, the majority with arteriosclerotic heart disease, and the effects on serum total cholesterol compared. L-thyroxin and each of the analogues studied, tetraiodothyroformic acid, dimethyldiiodothyroformic acid, D-thyroxin and D-triiodothyronine, were given to four to nine patients for periods up to 10 months.

At the doses employed each of the analogues resulted in a reduction in the mean level of serum cholesterol without obvious evidence of hypermetabolism or aggravation of angina pectoris or congestive heart failure. The reduced level of serum cholesterol was sustained throughout the period of hormone administration, and upon the substitution of a placebo returned to the pretreatment range.

L-thyroxin, at the dose employed, also effected a modest sustained reduction in serum cholesterol but both patients with angina included in this group experienced an increase in severity of symptoms.

Except for four patients who developed acneiform dermatitis, salivary gland swelling, or gastrointestinal symptoms during the administration of the formic acid analogues, no toxic or undesirable effects were observed from any of the analogues.

To evaluate better the general metabolic effects of the analogues each was administered to three or more of a group of seven myxedematous patients for periods of 6 to 12 months. Given in sufficient amount all were observed to increase basal metabolic rate and to maintain a clinically euthyroid state.

From these observations, it is concluded that the D-isomers of thyroxin and triiodothyronine, while not without general metabolic effects, are tolerated by the majority of euthyroid patients with coronary atherosclerosis in amounts sufficient to maintain a reduced serum cholesterol level.

Acknowledgment

The authors are grateful to Eli Lilly & Co. for supplies of tetraiodothyroformic acid, dimethyldiiodothyroformic acid, and D-thyroxin, to Baxter

Laboratories for D-thyroxin, and to Smith, Kline & French for D-triiodothyronine.

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Leopold Auenbrugger
1722—1809

We know to-day how important to medical science was Auenbrugger's discovery. In retrospect it is easy enough to perceive this. Nevertheless, we should be unjust to reproach Auenbrugger's contemporaries for having failed to recognize forthwith the value of percussion. Pathological anatomy was a new science, which had not yet secured general acceptance. The majority of doctors still regarded illnesses as essentially general, and thought that local conditions were subsidiary. Decades had still to elapse before anatomical outlooks secured general acceptance. As we shall see, it was left for French physicians in the beginning of the nineteenth century to realise that percussion was one of the most important methods of examination of the sick, as it has remained unto this day.—Henry E. Sigerist, M.D. *The Great Doctors.* New York, W. W. Norton & Co., Inc., 1933, p. 242.

Atherosclerosis in India

An Autopsy Study of the Aorta and the Coronary, Cerebral, Renal, and Pulmonary Arteries

By K. S. MATHUR, M.D., F.R.C.P., N. L. PATNEY, M.D., AND V. KUMAR, M.D.

ONE of the most important and potentially important facts about angina pectoris, coronary and cerebral thrombosis, intermittent claudication, and other clinical manifestations of atherosclerosis is the great difference in their incidence and mortality in different populations. Geographic differences have also been reported in the extent and severity of aortic and coronary atherosclerosis in different regions of the world.[1-4] Gore et al.[4] concluded from an analysis of autopsy material from South India (fig. 1) that atherosclerosis of the aorta and coronary arteries is remarkably mild in the population of that region as compared to that obtained in United States, Japan, and Jamaica. No other studies have been reported from India during recent years.

The present study was undertaken to assess the extent and severity of atherosclerosis in the aorta, coronary, cerebral, renal, and pulmonary arteries at Agra, an important medical center in Northern India. Such an approach may supply important clues to the etiologic significance of environmental factors in the pathogenesis of atherosclerosis.

Material and Methods

The material for study was obtained from 500 consecutive medicolegal autopsies performed at the Sarojini Naidu Medical College, Agra, on patients dying without morphologic evidence of atherosclerotic catastrophe, during the last 2 years. The distribution of these patients according to age and sex is given in table 1.

The following material was obtained for examination in each case: aorta, from the valvular ring to its abdominal bifurcation (right and left renal arteries were removed with the aorta, but all other branches were cut close to their aortic origins); heart with the coronary arteries, pulmonary trunk, and the right and the left pulmonary arteries; brain with its vessels in situ. These specimens were carefully washed with water and fixed in 10 per cent formalin.

The vessels were studied both before and after staining with Sudan IV. The methods described by the WHO study group[5] and Holman et al.[6] were utilized. The amount and severity of atherosclerosis was assessed by the method recommended by Gore and Tejada.[7] In brief, quantitative appraisal of atherosclerosis entails estimation of the extent of surface involvement of the intima in each artery. For this purpose the two renal arteries, the three major coronary arteries, and the arteries of the circle of Willis, as far as traced, were in each case regarded as a single channel. The decimal fraction of this involvement by each of the four grades of lesions was evaluated. These grades are characterized as grade I, lipid streaks, spots, or patches; grade II, fibrous and atheromatous plaques; grade III, necrotic, ulcerated, hemorrhagic or thrombotic plaques; and grade IV, calcified plaques. Surface involvement is estimated and recorded in one of the five groups: group O, less than 5 per cent surface involvement; group A, 6 to 15 per cent surface involvement; group B, 16 to 33 per cent surface involvement; group C, 34 to 50 per cent surface involvement; and group D, more than 50 per cent surface involvement. By grouping and grading both the extent of atherosclerosis and its character are expressed by a five-digit figure, the atherosclerotic profile, which is converted into an atherosclerotic index by appropriate weighting of the factors. The atherosclerotic index thus developed is a mathematical number ranging from 0 to 100, which is an expression of the amount and severity of atherosclerosis.

Results

The means of the atherosclerotic indices, along with the standard deviations and range for aorta, coronary, cerebral, and renal arteries, are given in table 2.

The atherosclerotic index of the aorta rose

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Table 1

Distribution of 500 cases by Age and Sex

Age group	No. of cases	Male	Female
0–10	42	32	10
11–20	65	41	24
21–30	139	102	37
31–40	109	80	29
41–50	71	49	22
51–60	47	33	14
61–70	22	16	6
71–80	5	4	1
	500	357	143

from a very low mean of 0.015 in the first decade to a maximum mean of 23.08 in the eighth decade. The disease appeared earliest at the age of 2½ years in a male child in the form of lipid spots at the supravalvular portion of the aortic ring. In the first decade 50 per cent of the aortas were completely free of atherosclerosis. In the second decade evidence of atherosclerosis in the form of fatty streaks was present in 95 per cent of the aortas. After the second decade the disease was seen in all the aortas. The average surface extent of the intimal involvement with atherosclerosis and the proportion involved by each of the four types of lesions are given in table 3

The surface extent of intimal alteration after the age of 30 years shows a progressive rise with age. The percentage of cases showing more than half of the intimal surface involvement increased from 4 per cent in the fourth decade to 25 per cent in the seventh decade. With increase in age the relative proportion of atherosclerotic lesions shifted toward an increase in the more advanced types. During the first decade the lipid streaks (grade-I lesions) predominated. The fibrous plaques (grade-II lesions) comprised 4, 6, and 24 per cent of the atherosclerotic process in the second, third, and fourth decades, respectively. The maximum surface involvement by the fatty streaks was observed in the third decade. Prior to the age of 40 years no calcified or complicated lesion was present. The incidence of lesions in grades II and IV increased from 4 per cent in the fifth decade to 24 per cent in the eighth decade. Meanwhile,

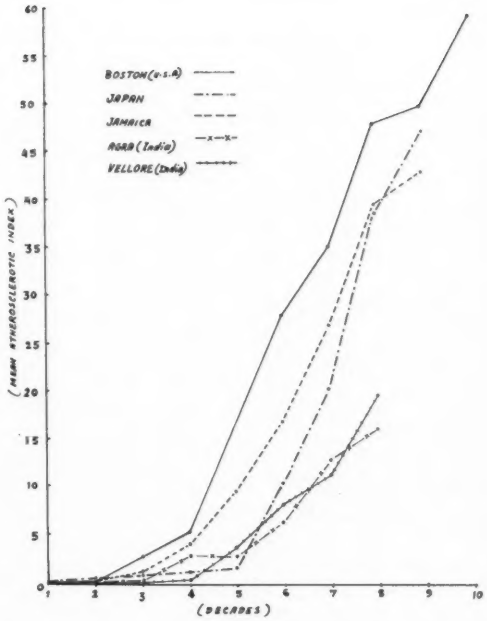

Figure 1

Progression of aortic atherosclerosis with age.

the fatty streaks progressively diminished so that in the eighth decade they comprised only 18 per cent of the atherosclerotic process.

Atherosclerosis of the Coronary Artery

Atherosclerosis of the coronary artery was first evident in the second decade in the form of lipid spots and streaks. After the fifth decade all the coronary arteries showed evidence of atherosclerosis.

The mean atherosclerotic index of the coronary arteries rose from 0.006 in the second decade to 21.53 in the eighth decade. The increase in the atherosclerotic index was especially marked after the fourth decade. There was no terminal decline in the mean atherosclerotic index.

When the data were analyzed for the extent of intimal surface involvement (table 4) the mean surface area of the coronary arteries involved in atherosclerosis increased with age, especially after the fourth decade.

In the seventh and eighth decades 10 per cent and 20 per cent of the cases had more than 50 per cent of intimal surface involve-

Table 2

Mean Atherosclerotic Indices of Aorta, Coronary, Cerebral, Renal, and Pulmonary Arteries for Each Decade

Age group (yrs.)	Mean age	Aorta	Coronary	Cerebral	Renal
0–10	5	0.015 ± 0.198 (0 — 0.03)*	—	—	—
11–20	17	0.105 ± 0.050 (0.03 — 1.23)	0.006 ± 0.064 (0 — 0.18)	—	0.013 ± 0.084 (0 — 0.13)
21–30	25	0.289 ± 0.280 (0.03 — 1.23)	0.032 ± 0.045 (0 — 0.18)	—	0.021 ± 0.041 (0 — 0.13)
31–40	36	0.839 ± 1.766 (0.03 — 5.30)	0.342 ± 1.186 (0 — 4.37)	0.013 ± 0.014 (0 — 0.18)	0.060 ± 0.102 (0 — 0.85)
41–50	46	3.090 ± 5.958 (0.12 — 15.30)	1.611 ± 1.903 (0 — 7.33)	0.090 ± 0.110 (0 — 1.09)	0.140 ± 0.034 (0 — 1.33)
51–60	57	7.583 ± 4.316 (0.15 — 39.93)	5.639 ± 7.993 (0.13 — 24.33)	0.477 ± 0.790 (0 — 1.33)	0.215 ± 0.430 (0 — 0.73)
61–70	66	11.412 ± 8.751 (0.33 — 24.30)	10.889 ± 9.038 (0.33 — 21.30)	1.014 ± 0.718 (0 — 1.33)	0.896 ± 0.260 (0.33 — 2.43)
71–80	75	19.53 ± 9.431 (3.33 — 37.93)	17.330 ± 8.531 (5.27 — 3.33)	2.015 ± 1.903 (1.33 — 3.33)	1.280 ± 1.703 (0.33 — 2.73)

*The figures in parentheses indicate range.

ment. As in the aorta, the relative proportions of the four grades of atherosclerotic lesions shifted toward the more advanced types with increasing age (table 4). Complicated and calcified lesions were seen for the first time in the fifth decade and together comprised 20 per cent of the atherosclerotic process. In the eighth decade, however, the complicated and the calcified lesions formed, respectively, 4 per cent and 19 per cent of the process.

Atherosclerosis of the Cerebral Artery

In the present series the incidence of cerebral atherosclerosis was much less than aortic and coronary atherosclerosis. No atherosclerotic lesions were seen in the first three decades. Fatty streaks were seen in the fourth decade and comprised 28 per cent of the total atherosclerotic process (table 5).

Fatty streaks increased to the sixth decade. Fibrous plaques were noticeable from the fourth decade, and their incidence increased from 2 per cent in the fourth decade to 67 per cent in the eighth decade. No complicated or calcified lesions were noted. The surface involvement with atherosclerosis increased gradually with age (table 5). In the seventh decade 45 per cent of cases showed 6 to 15 per cent of the total surface involvement with atherosclerosis. Though the percentage of cases showing evidence of cerebral atherosclerosis increased progressively with age, 16 per cent of the cases in the seventh decade were still free from any lesions.

The mean atherosclerotic index as in the case of the aorta and the coronary arteries showed a progressive rise with age; from 0.013 in the fourth decade to a maximum of 2.315 in the eighth decade.

Atherosclerosis of the Renal Artery

Evidence of atherosclerosis in the renal artery was first found in the second decade in the form of fatty streaks. The mean atherosclerotic index rose from 0.013 in the second decade to a maximum mean of 1.880 in the eighth decade. In the second decade, 43 per cent of cases showed renal artery atherosclerosis and 18 per cent of cases were still free of renal artery atherosclerosis in the sixth decade, whereas the disease was universal in the subsequent age groups. The mean surface involvement slowly progressed with age so that 50 per cent of cases had a surface involvement between 6 to 15 per cent in the eighth decade (table 6).

Table 3

Aortic Intimal Involvement with Atherosclerosis: Groups and Grades of Lesions for Each Decade

Age group (yrs.)	No. of cases	Group					Grade			
		O	A	B	C	D	I	II	III	IV
0–10	42	42	0	0	0	0	50	0	0	0
11–20	65	30	33	2	0	0	91	4	0	0
21–30	139	42	45	42	7	3	94	6	0	0
31–40	109	38	43	24	2	2	76	24	0	0
41–50	71	21	22	16	9	3	63	33	2	2
51–60	47	5	7	16	15	4	43	45	8	4
61–70	22	2	2	5	8	5	35	49	10	6
71–80	5	0	0	2	2	1	18	58	14	10

As in the other arteries the grades of atherosclerosis showed progressive, more advanced lesions with age. The fibrous plaques were first noted in the fourth decade and their incidence increased from 7 per cent of the atherosclerotic process in that decade to 59 per cent in the eighth decade. Calcified lesions were first observed in the sixth decade and comprised 1 per cent of the atherosclerotic process, whereas their maximum incidence was seen in the eighth decade.

Atherosclerosis of the Pulmonary Artery

No evidence of atherosclerosis of the pulmonary artery was found in any of the cases.

Comparison of the Mean Atherosclerotic Indices in Males and Females

The mean atherosclerotic indices of the aorta and the coronary, cerebral, and renal arteries in each decade for males and females have been tabulated (table 7).

It is seen that up to 30 years of age, the amount and severity of atherosclerosis in aorta and coronary arteries do not differ significantly. In the fourth decade the mean atherosclerotic indices of aorta and coronary arteries were 1.405 and 0.514, respectively, for males, and were 0.635 and 0.117, respectively, for females. The maximum atherosclerotic index of the aorta for females was much less than the average for males in the fourth decade. The same was true for the fifth decade. After the fifth decade the mean atherosclerotic index for females rose sharply from 0.77 and 0.63 for aorta and coronary arteries to 3.25 and 4.58 in the eighth decade, although here again the mean for the females was less than that for males. A similar relationship for the two sexes was maintained for these arteries up to the eighth decade. Thus after the third decade the mean atherosclerotic index for aorta and coronary arteries rose relatively gradually in males in successive decades while in females it showed a steep rise in the sixth decade. In the cerebral arteries too the mean atherosclerotic index was consistently lower in females than in males in each decade, though it progressed gradually through each successive decade after appearing in either sex in the fourth decade for the first time. No such relationship for the two sexes was evident for the renal arteries.

Discussion

Much of the past epidemiologic work on atherosclerosis has provided only circumstantial evidence because, until recently, no methods were available by which the actual morbid incidence of atherosclerosis in different groups or races could be compared. Availability of quantitative technics such as that of Gore and Tejada[7] should do much to substitute facts for assumptions.[8]

The results obtained from this study indicate that atherosclerosis in the aorta, coronary, cerebral, and renal arteries progresses with advancing age. The findings are in conformity with those of the previous workers.[1–4, 8–10]

Aortic atherosclerosis was evident in the first decade, and this constitutes the best evidence for the contention that atherosclerosis

Table 4

Coronary Artery Surface Involvement with Atherosclerosis: Groups and Grades of Lesions for Each Decade

Age group (yrs.)	No. of cases	Group					Grade			
		O	A	B	C	D	I	II	III	IV
0–10	42	42	0	0	0	0	0	0	0	0
11–20	65	65	0	0	0	0	19	0	0	0
21–30	139	123	16	0	0	0	64	2	0	0
31–40	109	93	12	4	0	0	53	38	0	0
41–50	71	38	20	13	0	0	35	56	3	1
51–60	47	14	17	14	2	0	31	65	2	2
61–70	22	4	10	4	2	2	20	70	3	7
71–80	5	0	1	2	1	1	11	66	4	19

Table 5

Cerebral Artery Surface Involvement with Atherosclerosis: Groups and Grades of Lesions for Each Decade

Age group (yrs.)	No. of cases	Group					Grade			
		O	A	B	C	D	I	II	III	IV
0–10	42	42	0	0	0	0	0	0	0	0
11–20	65	65	0	0	0	0	0	0	0	0
21–30	139	139	0	0	0	0	0	0	0	0
31–40	109	109	0	0	0	0	28	2	0	0
41–50	71	67	4	0	0	0	33	13	0	0
51–60	47	39	8	0	0	0	39	19	0	0
61–70	22	13	9	0	0	0	35	49	0	0
71–80	5	1	2	1	1	0	33	67	0	0

is not a disease of senescence.[11] Increase of the aortic atherosclerotic index, which is an expression of both the extent and severity of the disease, was gradual in the first three decades, but rapid thereafter. The slow rate of rise of the index in the earlier decades might be due to the low weights assigned to the grade-I lesions, which are the predominant components of the atherosclerotic process during that period. The absence of the step-like progression in the present study suggests that atherosclerosis does not develop in bouts, and that "episodic development" is not a feature of the disease.[11]

The progression of coronary atherosclerosis showed a rather steep rise after the fourth decade and it continued to increase through the eighth decade. Our findings thus fail to corroborate those of Ackerman et al.[12] and White et al.,[9] who observed a terminal decline in the incidence of coronary atherosclerosis. These authors attributed the decline to the elimination from the later decades through death of the more severely affected individuals, and suggested that the disease in the remaining persons might be progressing as before. It is suggested that such an elimination was not present to a sufficient degree in our study to affect significantly the mean coronary atherosclerotic index in the later decades. This might be due to a relatively low incidence of coronary atherosclerosis in the earlier decades in our cases as compared to the others.

Minimal atherosclerosis of the cerebral arteries was first evident in the fourth decade and, thereafter, a gradual progression was noticed up to the eighth decade. The concept that atherosclerosis in the cerebral arteries steadily progresses to a certain level and remains at about the same level throughout the remaining decades,[10] could not be substan-

Table 6

Renal Artery Atherosclerosis: Groups and Grades of Lesions for Each Decade

Age group (yrs.)	No. of cases	Group					Grade			
		O	A	B	C	D	I	II	III	IV
0–10	42	42	0	0	0	0	0	0	0	0
11–20	65	65	0	0	0	0	43	0	0	0
21–30	139	139	0	0	0	0	61	0	0	0
31–40	109	105	4	0	0	0	51	7	0	0
41–50	71	64	7	0	0	0	32	27	0	0
51–60	47	41	6	0	0	0	39	42	0	1
61–70	22	16	5	1	0	0	33	65	0	2
71–80	5	1	3	1	0	0	25	69	1	5

tiated. In the renal arteries, too, a gradual increase in the atherosclerotic index with age from the second through the eighth decade was evident. The grades of lesions, however, showed much less change from earlier, less advanced types to later, more severe and advanced types. Roberts et al.[13] also rarely found more than moderate atherosclerosis in the renal arteries.

No atherosclerotic lesions were observed in any of the 500 consecutive pulmonary arteries examined. The incidence of pulmonary atherosclerosis is relatively low.[13]

The differences in severity of atherosclerosis between males and females in the aorta, and coronary, and cerebral arteries were apparent early in life and were especially marked up to the fifth and sixth decade when the difference tended to diminish, owing to a steep rise in the female atherosclerotic index after the fifth decade. The differences between the two sexes were of a sufficient magnitude to place females of 10 to 20 years behind the males in the development of atherosclerosis. Similar findings of predominance of atherosclerosis in males over females have been reported by other workers.[9, 11]

Since the differences in the development of atherosclerosis were evident at a very early age, the underlying cause may lie in some inborn basic difference between the two sexes, such as the generally more rapid metabolism in the males. Structural,[14] hormonal,[15] and sociological[16] differences have also been considered in explaining this discrepancy. The rapid rise in the female atherosclerotic index after the fifth decade could be due to the withdrawal of the protective action of estrogens after the menopause.[17]

The earliest lesions of atherosclerosis were the fatty streaks, which were seen earliest in a 2½-year-old child, at the supravalvular portion of the aortic ring. Zinserling[18] had found these sudanophilic spots even in cases less than 3 years of age. There was a rapid rise in the incidence of fatty streaks around puberty, which might be related to the hormonal changes then occurring. The peak incidence of the fatty streaks in the aorta was in the third decade. The subsequent decline could be due to their conversion into fibrous plaques and not necessarily due to their regression.[19] The universality of fatty streaks after the second decade in the case of the aorta re-emphasizes the fact that all individuals belonging to later decades have aortic atherosclerosis but merely differ in the degree and severity of involvement. All these observations are in conformity with those of Holman et al.[19]

Fibrous plaques in the aorta appeared at the same anatomic sites as the fatty streaks did in the earlier decades. This supports the view that fatty streaks act as an anlage for the fibrous plaques.

Tejada and Gore[1] reported the occurrence of the grade-III lesions in the aorta in the third decade in white subjects and in the fifth decade in Negroes for the first time. In our series, they were seen first in the fourth decade, and their incidence increased with age.

In the coronary arteries the grade-III lesions constituted only about 4 per cent of the

Table 7

Mean Atherosclerotic Indices of Aorta, Coronary, Cerebral and Renal Arteries in Males and Females

Age group (yrs.)	Mean age		Aorta		Coronary		Cerebral		Renal	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
0–10	4	6	0.013 (0—0.03)*	0.012 (0—0.03)	— —	— —	— —	— —	— —	— —
11–20	17	17	0.107 (0.03—0.37)	0.085 (0—0.13)	0.008 (0—0.03)	— —	— —	— —	0.010 (0—0.03)	0.010 (0—0.03)
21–30	25	25	0.310 (0.03—1.23)	0.198 (0.03—0.63)	0.032 (0—0.18)	0.030 (0—0.13)	— —	— —	0.022 (0—0.13)	0.021 (0—0.13)
31–40	36	36	1.405 (0.03—5.30)	0.635 (0.03—4.37)	0.514 (0—2.74)	0.117 (0—0.85)	0.015 (0—0.13)	0.007 (0—0.03)	0.056 (0—0.27)	0.072 (0.03—0.85)
41–50	43	47	3.550 (0.12—15.30)	0.770 (0.27—2.33)	1.812 (0—7.33)	0.630 (0—133)	0.106 (0—1.09)	0.004 (0—0.03)	0.160 (0—1.27)	0.170 (0—1.33)
51–60	58	57	8.560 (0.15—38.93)	3.250 (0.15—10.13)	5.870 (0.13—12.93)	4.580 (0.27—12.93)	0.540 (0—1.33)	0.210 (0—0.33)	0.230 (0.03—0.73)	0.130 (0—0.68)
61–70	66	68	12.230 (0.33—24.30)	7.330 (0.68—13.30)	11.360 (0.53—21.30)	8.530 (0.38—13.30)	1.150 (0.03—1.33)	0.330 (0—0.93)	0.832 (0.33—1.83)	1.210 (0.33—2.43)
71–80	76	73	21.530 (3.33—37.93)	16.450 (—)	20.330 (5.27—33.30)	15.790 (—)	2.430 (1.33—3.30)	1.300 (—)	1.330 (0.30—2.73)	1.830 (—)

*The figures in parentheses indicate range.

atherosclerotic process whereas no grade-III or grade-IV lesions were found in our series in any of the cerebral arteries.

Summary

Striking differences in the extent and severity of atherosclerosis were observed when our results were compared with those reported from the United States, Japan, and Jamaica, and South India by Gore et al.[4] Up to the age of 30 years the mean atherosclerotic indices of aorta from these sources were not significantly different. Subsequently, however, the mean atherosclerotic index in our cases was almost equal to that reported from South India but it was much less than that recorded in the U.S.A. and significantly less than that reported from Japan and Jamaica. It is thus seen that the factors that initiate atherogenesis are different from those that are effective in the formation of the later grades of lesions, since the same amount of streaking does not lead to an equal amount of fibrous plaque formation. It also shows that there are important geographic differences in the prevalence of these latter factors. Similarly, the coronary atherosclerosis was almost equal in our and the South Indian series but in both these places it was less advanced than that obtained in the U.S.A., Japan, and Jamaica.

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Blood Pressure during Supine Exercise in Idiopathic Orthostatic Hypotension

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IDIOPATHIC orthostatic hypotension is characterized by an excessive fall in arterial blood pressure on standing and by other manifestations of an extensive loss of autonomic nervous function.

In the present study the arterial blood pressure was measured in seven patients with orthostatic hypotension during the performance of mild leg exercise in the supine position. The finding of a pronounced fall in blood pressure during and immediately after the exercise indicates that there is a major disturbance in the control of blood pressure even in circumstances in which gravitational factors are excluded.

Method

The group of patients with idiopathic orthostatic hypotension comprised four men and two women aged 50 to 61 years (table 1, cases 1 to 6). Studies were performed also in a man aged 44 years who had recently undergone thoracolumbar sympathectomy for essential hypertension (table 1, case 7).

The patients exercised by pedaling a cycle ergometer while in the supine position with the supporting table horizontal. On four occasions the exercise was repeated with the table tilted downward 15 degrees at the head end. Because most of the patients suffered from muscular weakness even when in the supine position, the exercise performed was mild, and it was carried out in periods of about 2 minutes. Oxygen consumption was measured in the two fittest patients during more prolonged periods of exercise; in the first patient (case 3), it increased from a resting value of 250 to 740 ml. per minute and in the second (case 5), from 260 to 530 ml. per minute. Oxygen consumption was not measured in the remaining patients owing to the mildness, brevity, and occasional irregularity of the exercise, but it was not likely to have increased by more than 100 per cent. The blood pressure was recorded from the radial artery by a Statham strain-gage transducer. The mid-chest level was taken as the zero reference point.

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Supported in part by research grant H-4744 from the National Institutes of Health, U. S. Public Health Service.

Results

The blood pressure in the supine position was within normal limits for the age in six patients, ranging from 135 to 160 mm. of mercury systolic and 60 to 85 mm. of mercury diastolic; in the other patient it was 185/100 (table 1). The pressures measured with the head end of the table tilted downward by 15 degrees were similar to those recorded in the horizontal position.

During exercise in the horizontal position the arterial blood pressure was unchanged in one patient (case 5). The other patients showed striking falls in both systolic and diastolic pressures (figs. 1-3). The pressure began to increase again in three patients (cases 3, 4, and 7) about 30 seconds after exercise was stopped, and it returned to the original level within 5 minutes. In the other three patients (cases 1, 2, and 6), however, it continued to fall for 20 seconds or more after the exercise was stopped. In the four patients tested, a fall of comparable magnitude occurred while the same exercise was performed with the table tilted 15 degrees downward at the head end (table 1 and figs. 2*b* and 3*b*).

Discussion

The abnormality of the arterial blood pressure in patients with orthostatic hypotension becomes evident on changing from the supine to the standing position (table 1). Further evidence that the patients in the present study had severe loss of autonomic nervous function

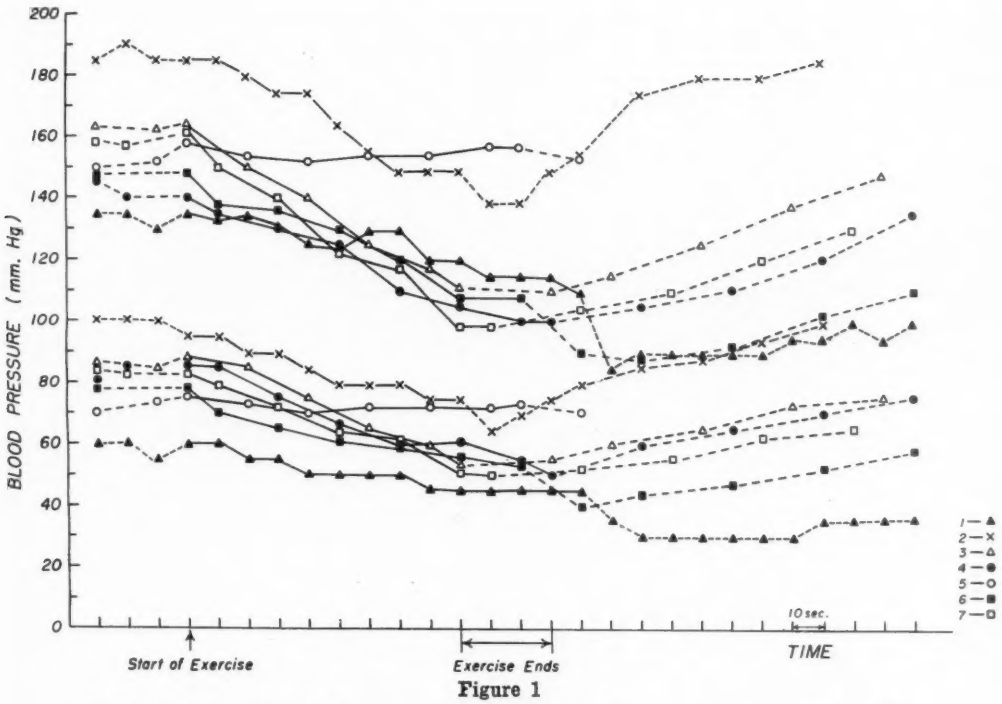

Figure 1

Systolic and diastolic blood pressures at radial artery during exercise in supine position (horizontal). Continuous line: *during exercise.* Interrupted line: *before and after exercise.*

was obtained from the response to the Valsalva maneuver (fig. 4). Following release of the raised intrathoracic pressure no "overshoot" of the arterial blood pressure occurred; instead, it returned slowly to its original level. A similar response was described previously in orthostatic hypotension[1, 2] and in other conditions involving interruption of autonomic nervous pathways, such as tabes dorsalis[3] and diabetic neuropathy,[4] as well as after thoracolumbar sympathectomy or the administration of ganglion-blocking agents.[2]

Table 1

Arterial Blood Pressure at Rest and During Exercise in Patients With Orthostatic Hypotension

Patient	Age, yr.	Sex	Supine, horizontal (mm. Hg)		Supine, 15 degrees head down (mm. Hg)		Standing (mm. Hg)
			Rest	Exercise*	Rest	Exercise*	
1	55	M	135/60	90/30	—	—	60/40
2	50	F	185/100	140/70	—	—	70/45
3	52	M	160/85	110/55	160/85	110/50	25/15
4	61	M	140/85	100/50	145/70	95/45	40/25
5	58	F	150/70	155/70	—	—	65/40
6	61	M	150/80	90/40	145/80	95/50	70/40
7†	44	M	160/85	100/50	165/80	115/55	70/40

*Values are lowest values obtained during, or shortly after termination of, exercise.

†This patient had orthostatic hypotension after thoracolumbar sympathectomy for hypertension.

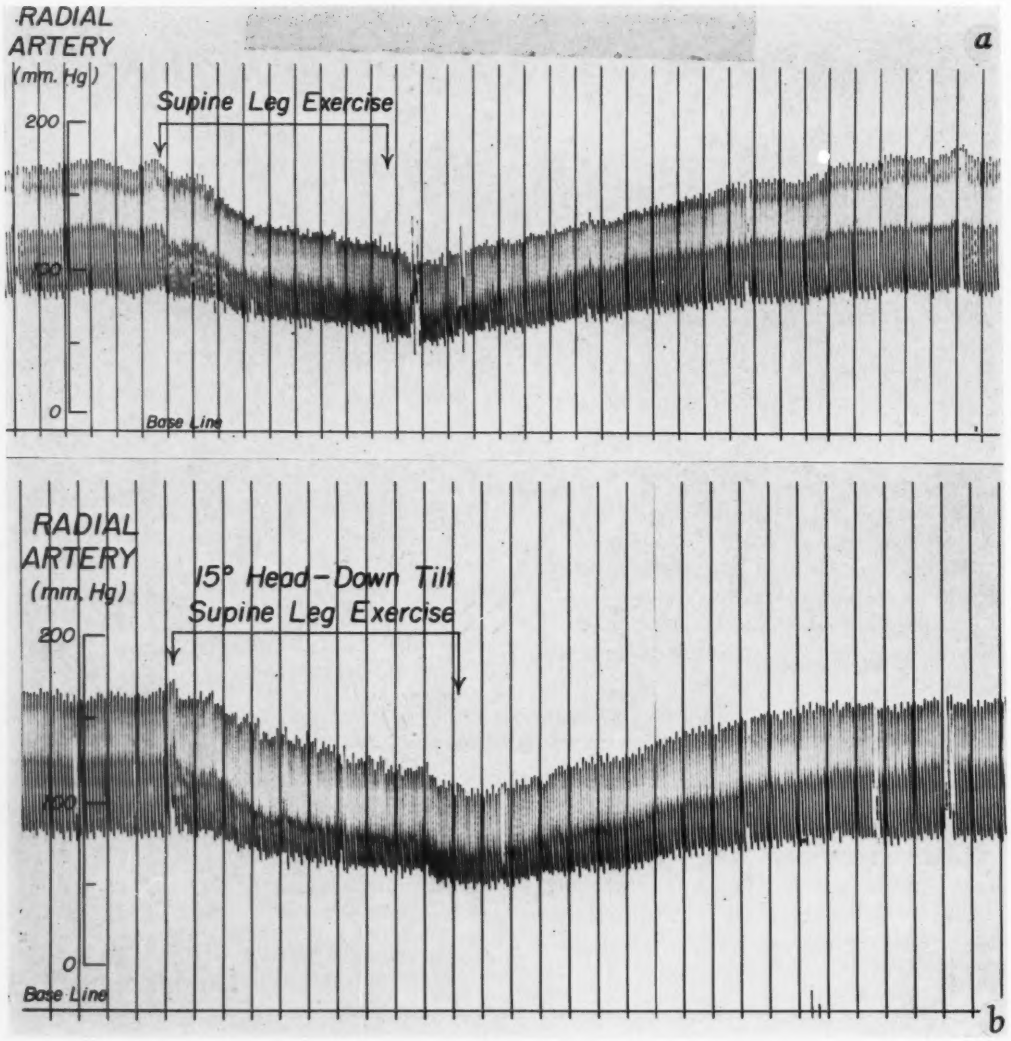

Figure 2

Case 3. Blood pressure during exercise in supine position in a patient with idiopathic orthostatic hypotension. a. *Horizontal supine position.* b. *Supine position with 15-degree head-down tilt. Vertical lines are at 10-second intervals.*

The finding in five of six patients with idiopathic orthostatic hypotension of a pronounced fall in blood pressure during mild leg exercise in the supine position, in which the effect of gravitational forces on the circulation is minimized, was unexpected. Indeed, a similar fall in blood pressure occurred during exercise performed with the head end of the table tilted downward; in this position the return of blood from the legs to the heart is aided by gravity. In normal persons compensatory constriction occurs in resting vascular beds during muscular exercise.[5, 6] It may be that in patients with orthostatic hypotension this regulatory system is abolished,[1] so that the net peripheral resistance is lower than in

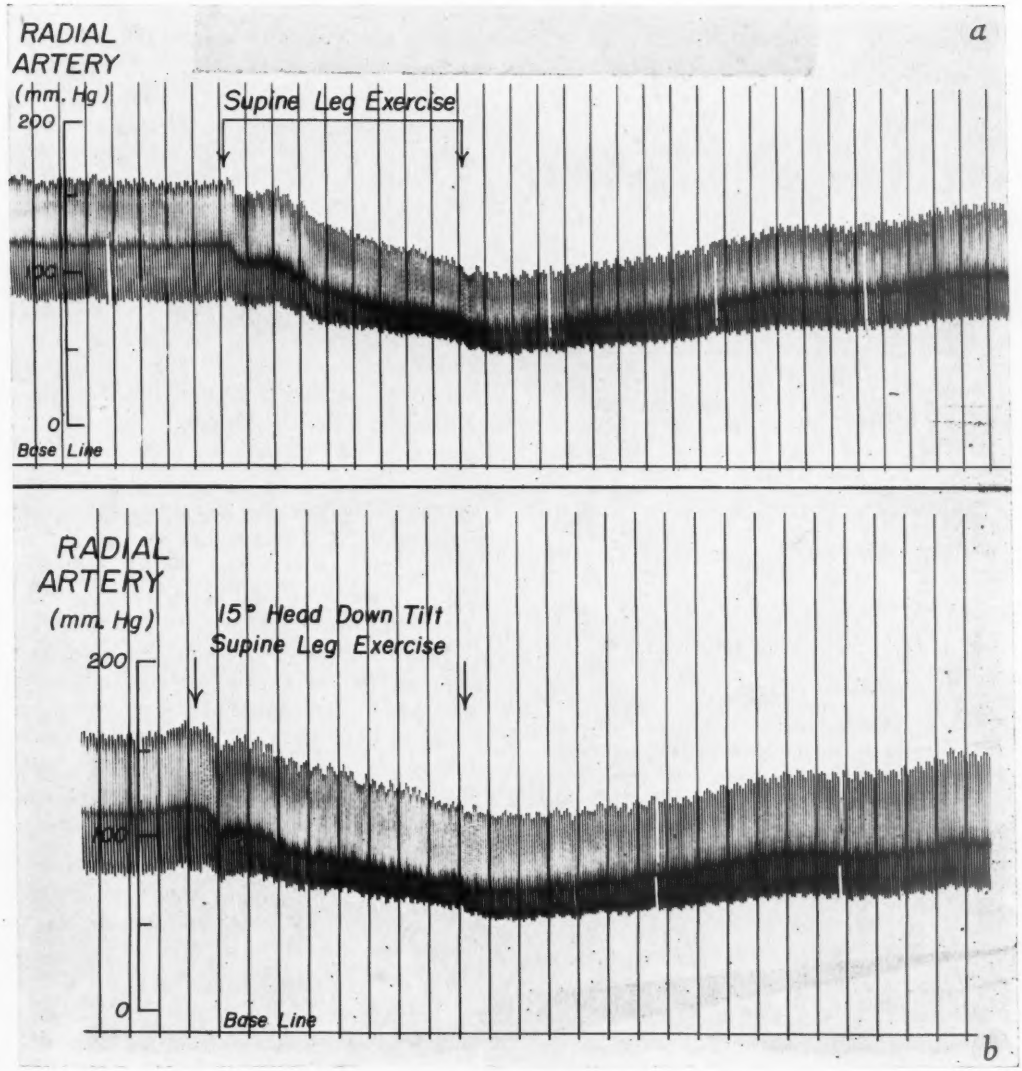

Figure 3

Case 7. Blood pressure during exercise in supine position in a patient who had had thoracolumbar sympathectomy. a. *Horizontal supine position.* b. *Supine position with 15-degree head-down tilt. Vertical lines are at 10-second intervals.*

normal persons performing comparable exercise. Similar falls in systemic arterial blood pressure have been noted during supine leg exercise after administration of the adrenergic-blocking agents guanethidine[7] and bretylium tosylate.[8]

An additional factor that had to be considered was the possibility that partial or complete denervation of the heart prevented an adequate increase of cardiac output during exercise. Therefore, in two patients the cardiac output was measured during the second minute of exercise by the indicator-dilution method. In one of these patients

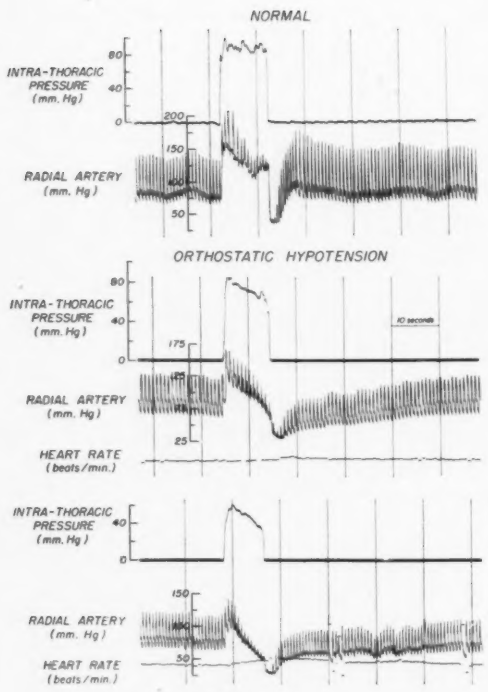

Figure 4

Effects of Valsalva maneuver in a normal subject (upper) *and in two patients (cases 4,* center, *and 6,* lower*) with idiopathic orthostatic hypotension.*

(case 3), cardiac output increased from 4.7 to 6.4 liters per minute and in the other (case 5), from 6.8 to 8.8 liters per minute. These increases were of the same order as those obtained in normal subjects performing similar mild exercise. In the patient who had had thoracolumbar sympathectomy and in whom the reflex nervous pathways to the heart were intact, the similar fall in pressure during exercise must have been caused solely by the failure of compensatory constriction of other vascular beds.

The effect of exercise in the supine position on arterial blood pressure in patients with orthostatic hypotension can be contrasted with that observed in patients with severe mitral stenosis. In the latter condition the cardiac output may be incapable of increasing; however, despite dilatation of vessels in the active skeletal muscles, the blood pressure is well maintained owing to compensatory constriction in other vascular beds.[5]

Thus, although arterial blood pressure depends on both cardiac output and peripheral resistance, the results of this study suggest that the reflex coordination of the various vascular beds plays the major role in maintaining arterial pressure.

Summary

The arterial blood pressure was measured during exercise in six patients with idiopathic orthostatic hypotension. In five there was a pronounced fall of arterial pressure while the subjects exercised in the supine position on a horizontal table. The systolic and diastolic pressures fell by an average of 50 and 32 mm. of mercury, respectively. During comparable exercise with the table tilted 15 degrees head downward, the pressures fell to a similar degree. Thus, an abnormal response of blood pressure occurred under conditions in which venous pooling was unlikely to be present.

It is suggested that the fall in blood pressure during exercise in the supine position was the result of failure of compensatory constriction of other vascular beds and not of failure of the cardiac output to increase. Thus, the net peripheral resistance in such patients is less than that in normal persons performing comparable exercise.

Acknowledgment

We wish to thank Dr. E. A. Hines, Jr., for his interest and cooperation.

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On Percussion of the Chest

First Observation

OF THE NATURAL SOUND OF THE CHEST, AND ITS CHARACTER IN DIFFERENT PARTS

I. The thorax of a healthy person sounds, when struck. I deem it unnecessary to give in this place any description of the thorax. I think it sufficient to say that, by this term, I mean that cavity bounded above by the neck and clavicles, and below by the diaphragm: in the sound state, the viscera it contains are fitted for their respective uses.

II. The sound thus elicited (1) from the healthy chest resembles the stifled sound of a drum covered with a thick woollen cloth or other envelope.

III. This sound is perceptible on different parts of the chest.—From *On Percussion of the Chest.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 125.

A Method of Photographing Fluorescence in Circulating Blood in the Human Retina

By HAROLD R. NOVOTNY, B.S., AND DAVID L. ALVIS, M.D.

THE PHYSIOPATHOLOGY of the retinal vasculature would be better understood if more were known about blood flow in these vessels. Because of the unique quality of transparency in the eye, methods depending on direct observation of the retinal vessels seem especially inviting. Already reported by various authors are technics for measuring the changes in caliber of retinal vessels,[1] and methods of observing retinal blood flow by cinematography,[2] and, in cats, by injecting trypan blue.[3] Although useful, these methods have certain limitations, and additional means of observing retinal blood flow with increased visibility and definition are needed.

The purpose of this paper is to describe a method for the study of retinal blood flow in man by the use of intravascular fluorescein and retinal photography, and to report some preliminary observations made with this method.

Materials and Methods

The Zeiss fundus camera was used. It was equipped with an electronic flash, the maximum discharge of which allowed one photograph every 12 seconds. Light intensity of the electronic flash was set at position III, and retinal photographs were made of the luminescence of fluorescein as it passed through the retinal vessels. In order to do this, both activating and emitting wave lengths of blood-fluorescein mixtures were determined spectrofluorometrically. The optimal activating wave length was found to be 490 mμ, in the blue range of the visible spectrum; and the maximal emitting wave length was 520 mμ, in the green. Kodak wratten filters no. 47 and no. 58, combined with a 3-mm. layer of 0.25 M copper sulfate, were accordingly inserted into the optical system (figs. 1 and 2) at appropriate points.

In order to modify the activating light, the blue no.-47 filter was placed in the path of the beam from the electronic flash and from the incandescent viewing source. This made it possible to see, as well as to photograph, the fluorescence as it developed and faded.

The green no.-58 filter with the copper sulfate layer was placed in the path of emitted light in order to absorb background illumination and increase the contrast between it and the transmitted fluorescence. The green no.-58 filter permitted approximately 5 per cent transmittance in the blue range, which gave a visible background in the retinal photograph irrespective of the fluorescence. The layer of copper sulfate solution was not essential, but slightly sharper negatives were obtained with it.

Anseo Super Hypan 35-mm. film was used; it was force developed for 10 minutes at 70 F. with UFG Ethol developer, placed in an acetic acid stop bath, and fixed for 10 minutes with Kodak acid fixer. Prints were made on Kodak Medalist F-2 or F-4 photographic paper, depending on the contrast desired.

In each patient, a control picture of the fundus was taken prior to injection of fluorescein. Then, in a darkened room, 5 ml. of Fluorescite* were rapidly injected into an antecubital vein and were followed by 5 ml. of normal saline to deliver a concentrated bolus of dye into the circulation. The first photograph was made when arterial fluorescence appeared, followed by serial photographs at 12-second intervals for approximately 3½ minutes.

Results

Normal Patients

The time from injection into the antecubital vein until visualization of fluorescence varied from 12 to 30 seconds, when a striking lumi-

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Supported in part by contract AF 41 (657-225) monitored by the School of Aviation Medicine, Brooks Air Force Base, Texas, in part by grants from the Life Insurance Medical Research Fund and the Knights Templar Eye Foundation, and in part by grant 2B5034, U. S. Public Health Service.

*Fluorescite is 5 per cent fluorescein in sodium bicarbonate, an injectable product of the C. F. Kirk Company, 521 W. 23rd St., New York 11, New York.

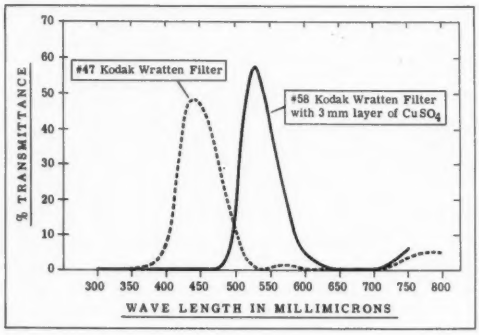

Figure 1

Percentage transmittance of filters used in the camera.

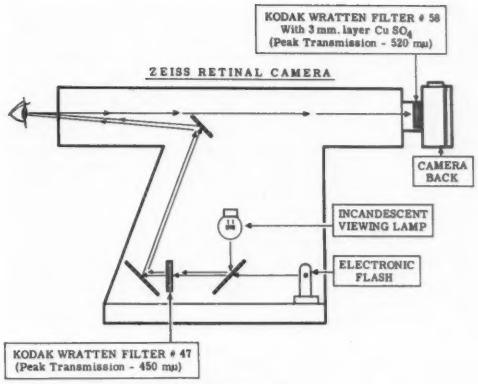

Figure 2

Cross section of optical system of Zeiss fundus camera with filters inserted.

nescence appeared in the retinal vessels as the fluorescein passed through them.

Separate arteriolar and venous filling phases were present in the serial photographs (figs. 3 and 4). During and after the venous filling phase, a generalized background mottling developed, presumably representing the choroidal circulation. Near the end of the 3½ minute period of photography, contrast faded and the retinal vessels were difficult to see.

There were considerable differences in the circulation times from arteriolar to venous sides in different portions of the retina, the arteriovenous transit time being fastest in the region of the fovea, and slowest in the peripheral portions of the retina. An occasional arteriolar twig emptied more slowly than the others of similar size at comparable distances from the disk. One arteriolovenous shunt was seen.

Stratified flow occurred in many of the larger vessels. In the larger arterioles the flow rate seemed more rapid in the central portion of the vessel than along the walls, since fluorescence appeared first and cleared first in the central portions. In the larger veins there was often a reversal of this pattern, the lateral portions of the venous stream first showing fluorescence, sometimes on only one side of the vein, as fluorescent blood entered the vein from small branches near the disk. These fluorescent streams tended to maintain their lateral position along the same side of the vein all the way to the disk. Two or three minutes after the injection, some larger veins continued to show more prominent residual fluorescence along the walls than in the central portions. It was not clear whether this represented a fluorescent plasma cuff or fluorescence of the vessel wall itself.

Hypertensive and Diabetic Patients

In addition to the same findings as in the normal eye, fluorescence in some hypertensive and diabetic patients showed smaller, more obscure vascular patterns that were difficult or impossible to see with the ophthalmoscope or in ordinary retinal photographs. New vessel formation was one of the most striking findings in these patients. Fluorescence appeared in microaneurysms, vasoproliferative areas, and tortuous small vessels as well as in the normal circulation (figs. 5 and 6). Fluorescence could not be seen in hemorrhagic areas, although it appeared early in some cotton-wool patches and remained throughout the period of photography. Some patches and edema residues failed to become fluorescent.

Discussion

Serial fluorescence-photography of the human retinal vasculature provides a dynamic record and increased visibility of the vascular pattern and blood flow by means of a simple technic.

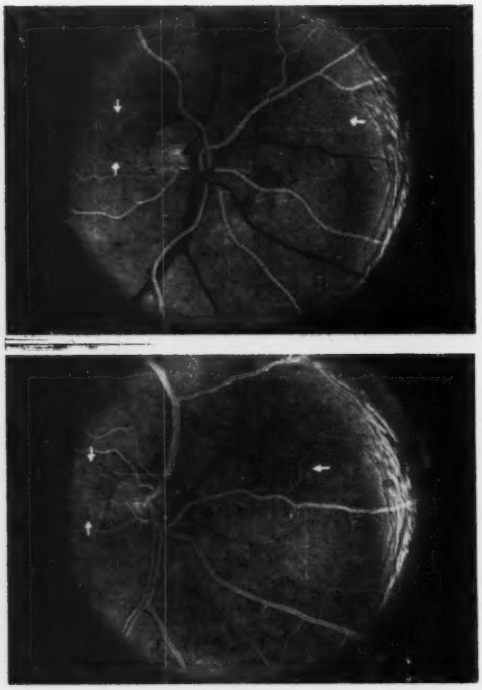

Figure 3

Normal patient. Top. *The arteriolar filling phase.* Bottom. *the venous filling phase. Arrows on the left indicate differential emptying of comparable-sized arterioles, and the arrow on the right indicates the rapid passage of the dye from an arteriole to a venule through a small vessel resembling an arteriolovenous shunt.*

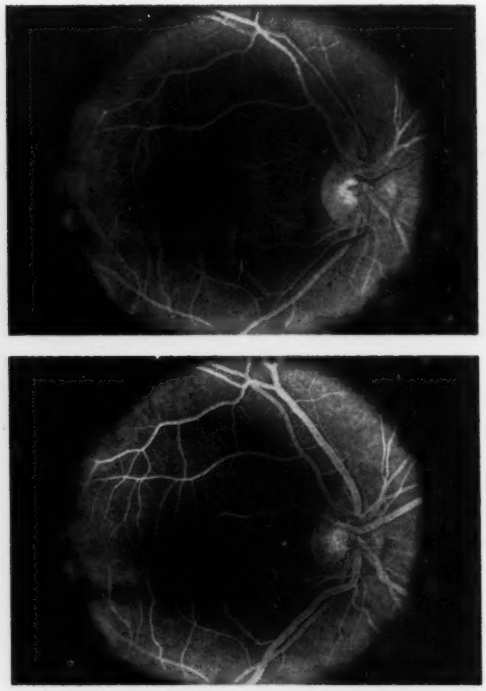

Figure 4

Normal patient. Top. *Arteriolar filling phase with laminar flow in the veins.* Bottom. *The venous filling phase.*

Activation by ultra-violet light was found to be unnecessary; filtered visible light avoided the potential hazards of ultra-violet exposure, and the natural fluorescence of the lens was no problem. The eventual appearance of fluorescein in the aqueous humor, however, contributed to the loss of definition in later serial photographs.

The background mottling, presumably from the choroidal circulation, which persisted throughout the period of photography, suggested that the rate of fluorescein turnover in the choroid may be slower than that of the retina.

At present, owing to the limitations of the electronic flash apparatus, pictures cannot be taken more often than every 12 seconds. A new incandescent light source and a rapid film-changer may eventually permit exposure to be made in more rapid succession. Also, retinal cinematography[2] would seem particularly adaptable to this method.

Further studies with the technics described here are being carried out to determine the rate of change of optical density of veins in the photographic negatives, to determine whether a relationship can be established between dye concentration and image density of the vessel. While such a relationship cannot give an estimate of retinal flow in absolute terms, it could provide a ratio between flow in control and experimental states, or between flow rates in different veins of the same eye.

Summary

A simple method, with use of intravenous fluorescein, was used for producing and photo-

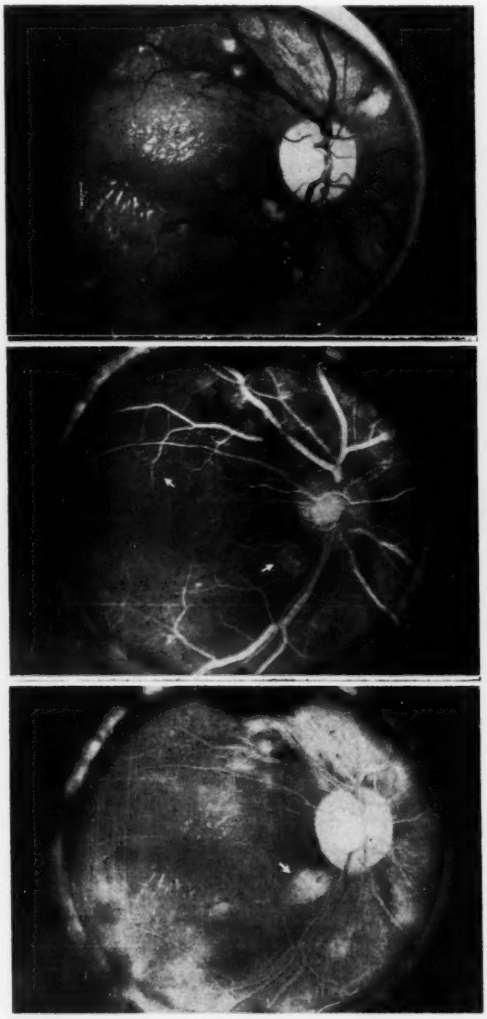

Figure 5

Hypertensive patient. Top. *Made with Kodak Plus-X film before the injection of fluorescein.* Middle. *Made with Super Hypan film and shows the venous filling phase.* Bottom. *Taken 3½ minutes after injection. The arrow near the optic nerve head (middle figure) points to a cotton wool exudate that is becoming fluorescent and that develops marked fluorescence in the bottom figure. The second arrow (middle figure) indicates a region that shows only a few scattered hemorrhages in the nonfluorescent picture (top figure) but that develops definite fluorescence (middle and bottom figures), suggesting that capillaries throughout the region may have abnormally great permeability. Several other regions of increased permeability are evident.*

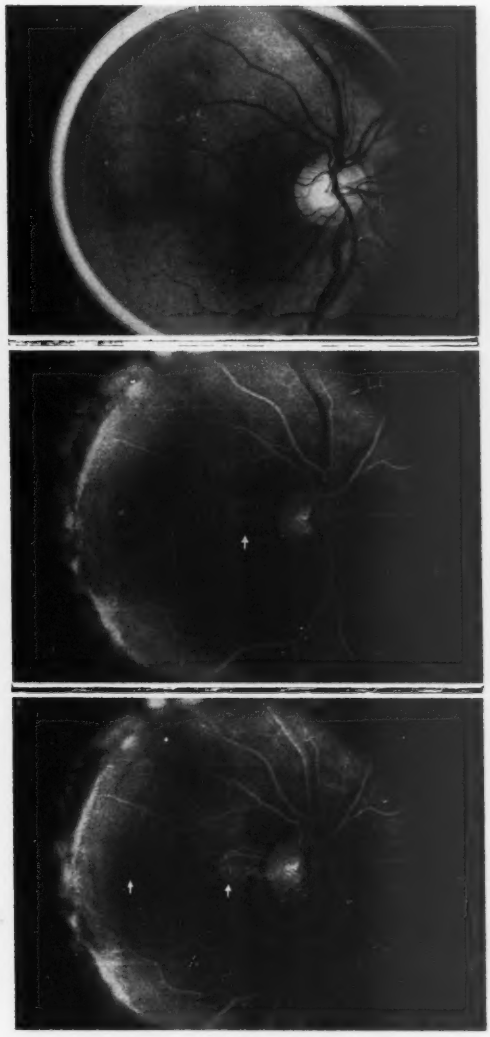

Figure 6

Diabetic patient. Top. *Made with Kodak Plus-X film before the injection of fluorescein.* Middle. *The arteriolar filling phase. The arrow points to a region of neovascularization and increased capillary permeability.* Bottom. *Venous filling. The arrow more distant to the disk indicates three microaneurysms that have become fluorescent.*

graphing fluorescence in circulating blood of the human retina.

Separate arteriolar and venous filling phases, an arteriolovenous shunt, sluggish choroidal circulation, stratified flow of fluo-

rescein, and rapid central retinal circulation times were observed in normal retinas.

Similar findings were seen in hypertensive and diabetic patients, and, in addition, neovascularization was clearly defined, and some cotton-wool patches, but not hemorrhages, were found to fluoresce.

Limitations and applications of the method are discussed.

Acknowledgment

Grateful appreciation is extended to John B. Hickam, M. D., and Fred M. Wilson, M. D., of the Departments of Medicine and Ophthalmology, respectively, for their assistance and criticism. The work of James Hartigan and others at Eli Lilly Company in determining spectrofluorometric data was most helpful.

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THIRD OBSERVATION

Of the Preternatural or Morbid Sound of the Chest and Its General Import

X. To be able justly to appreciate the value of the various sounds elicited from the chest in cases of disease it is necessary to have learned, by experience on many subjects, the modifications of sound, general or partial, produced by the habit of the body, natural confirmation as to the scapulae, mammae, the heart, the capacity of the thorax, the degree of fleshiness, fatness, etc., inasmuch as these various circumstances modify the sound very considerably.—From *On Percussion of the Chest.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 127.

Plasma Lipoprotein Lipase after Subcutaneous Heparin

By WILLIAM E. CONNOR, M.D., AND MARK L. ARMSTRONG, M.D.

IN ADDITION to its anticoagulant action, heparin initiates the release of lipoprotein lipase into the blood. This lipolytic enzyme has the capacity to reduce the turbidity of lipemic plasma and hence has become known also as "clearing factor." Its clearing action occurs from the hydrolysis of triglyceride contained in chylomicrons and other lipoprotein particles.[1]

Studies in animals have suggested that the administration of heparin inhibited the development of atherosclerosis.[2-4] Heparin may block atherogenesis because of its antilipemic property. Heparin has been used in the treatment of patients with coronary atherosclerosis because of these effects on lipid metabolism.[5-7] Lipoprotein lipase resulting from the injection of heparin reduces lipemia[8] and thereby may inhibit atheroma formation.

It is known that this enzyme appears in the blood promptly after the intravenous injection of heparin and begins to disappear rapidly.[9] In order to obtain more prolonged activity, heparin has been given by subcutaneous injection..

The present investigation was undertaken to find out how long lipoprotein lipase remained in the blood of men after the administration of subcutaneous and intravenous heparin. If the use of heparin in the therapy of atherosclerosis is predicated on its antilipemic action, then it would seem of some importance to show the particular dose as well as the route of administration that can be expected to produce significant and prolonged plasma lipoprotein-lipase activity. The influence of age, disease, and long-term heparin administration upon the lipoprotein-lipase response to subcutaneous heparin was studied also.

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Supported by research grants from the National Institutes of Health and the Iowa and American Heart Associations.

Materials and Methods

All subjects were men in good nutritional status. Pre-heparin blood studies were performed before breakfast. For subcutaneous administration, heparin was then injected into the upper outer arm through a 25-gage needle. Heparin* was given subcutaneously in all instances except as indicated. Intravenous heparin was given over a 5-minute interval. Subsequently, the subjects had their usual meals. Subjects were divided into three groups.

Nineteen men, aged 22 to 71 years with a mean age of 43, received 50 mg. (5,000 units) of heparin (group A). Six were healthy prison volunteers, aged 22 to 26 years. Six, aged 33 to 64, had known coronary atherosclerosis; four, aged 36 to 71, had cerebral vascular disease. Three, aged 24 to 64, were healthy or had minor disorders.

Seven other subjects, aged 40 to 63, received 200 mg. (20,000 units) of heparin in two different concentrations 1 week apart (group B). The concentrations used were 100 mg. per ml.* and 400 mg. per ml.† These men had a variety of illnesses: only one had coronary atherosclerosis, another had hypertension, and the remainder did not have vascular disease. No subject in any group had cardiac failure, clinically evident renal disease, or a metabolic disease besides atherosclerosis.

The effects of the same dose of heparin (50 mg.) given by the intravenous and subcutaneous routes were compared on different days in two subjects of group A.

Eight men who had received 50 mg. of subcutaneous heparin daily for periods of 9 to 17 months were tested for lipoprotein-lipase response to heparin (group C). They had either coronary atherosclerosis with a documented myocardial infarction or cerebral vascular disease. In preparation for the test they had omitted their usual heparin for 36 hours. In the morning each was given 50 mg. of heparin.

*Sodium heparin, The Upjohn Company, Kalamazoo, Michigan.

†Sodium heparin, Abbott Laboratories, North Chicago, Illinois.

Table 1

Plasma Lipoprotein Lipase after 50 mg. of Heparin Given by Subcutaneous Injection (Group A)*

Number of subjects	Hours after heparin	Glycerol (μM per ml.) Mean	S.D.	p	Change in optical density (units) Mean	S.D.	p
12	0	0.017	0.021		0.057	0.033	
	8	0.543	0.198	< 0.001	0.269	0.067	< 0.001
7	0	0.020	0.045		0.029	0.022	
	12	0.263	0.067	< 0.001	0.180	0.038	< 0.001
13	0	0.015	0.034		0.037	0.032	
	16	0.334	0.080	< 0.001	0.199	0.065	< 0.001
7	0	0.020	0.045		0.029	0.022	
	20	0.239	0.058	< 0.001	0.157	0.081	< 0.01
19	0	0.018	0.031		0.047	0.032	
	24	0.150	0.120	< 0.001	0.094	0.050	< 0.01

*The values for lipoprotein lipase obtained before heparin (at 0 hour) are compared with those occurring after heparin at various intervals of time. Each of the 19 subjects had a pre-heparin determination and two or more post-heparin determinations.

Measurement of Lipoprotein Lipase

Blood samples were obtained from forearm veins, and 9 ml. of blood were added to 1 ml. of 1.85 per cent potassium oxalate solution in tubes chilled in an ice bath. Specimens were centrifuged at 4,000 rpm and 4 C. for 10 minutes. Subsequently, the plasma specimens were kept at 4 C. for a period not longer than 2 hours before enzymatic activity was determined. The enzyme remains stable in plasma for over 4 hours at 4 C.

Plasma lipoprotein lipase was measured by two methods: by the amount of glycerol produced by lipolytic action, and by the reduction of optical density or "clearing" of a plasma-coconut oil emulsion. These methods have been described in detail.[10]

The whole-blood clotting time was measured by the method of Lee and White with three clotting tubes.[11]

Results

Comparison of the Plasma Lipoprotein Lipase after the Intravenous and Subcutaneous Injection of Heparin

After 1 hour heparin given intravenously stimulated an initially greater lipoprotein-lipase response than did subcutaneous heparin. By 6 hours the effect had disappeared completely. In contrast, subcutaneous heparin of the same dosage caused an increase in plasma lipoprotein lipase, which persisted for at least 24 hours and probably up to 36 hours (fig. 1). A similar result was obtained in the other subject so tested.

Duration of Action of Subcutaneous Heparin, 50 Mg. (5,000 Units)

In 19 subjects of group A, plasma lipoprotein lipase was determined before and after the subcutaneous injection of 50 mg. of heparin. Table 1 gives the mean values of the two indices for lipoprotein-lipase activity: glycerol production and the change in optical density of the incubation mixture. Both glycerol and optical density change were increased significantly at 8, 12, 16, 20, and 24 hours after heparin. Some decline in lipoprotein-lipase activity occurred between 8 and 12 hours, but there was little change from 12 to 20 hours after heparin. At 24 hours lipoprotein lipase was still present in the plasma at a significant concentration for both glycerol production and optical density change. The decline from 8 to 24 hours was 23 per cent for glycerol and 22 per cent for optical density change. Figure 2 shows graphically the net increases in plasma lipoprotein lipase after subcutaneous heparin as compared with the control level.

Influence of Disease and Age upon the Lipoprotein-Lipase Response to Subcutaneous Heparin (Group A)

Ten subjects had coronary or cerebral atherosclerosis. The lipoprotein-lipase response of these subjects at 16 and 24 hours after heparin was compared with the response in the eight healthy individuals (table 2). There

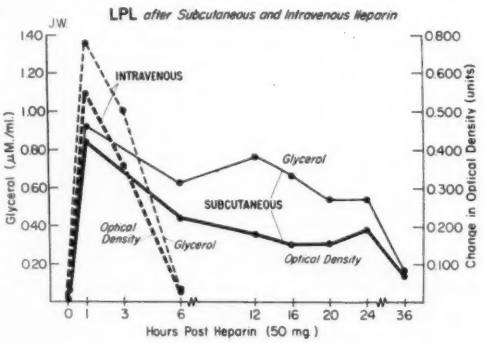

Figure 1

Plasma lipoprotein lipase (LPL) was measured after the injection of heparin in a 43-year-old man with clinically severe coronary atherosclerosis. Heparin in a dose of 50 mg. was administered intravenously on one day and then subcutaneously 1 week later.

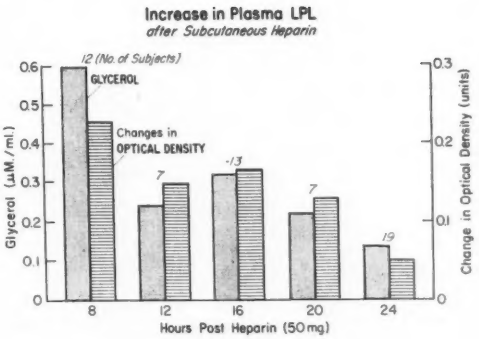

Figure 2

The net increase in plasma lipoprotein lipase (LPL) after the subcutaneous injection of 50 mg. of heparin. The values for glycerol and optical density change were obtained by subtracting the pre-heparin results (0 hour) from the post-heparin figures at the indicated times, thus giving the net increases.

were no significant differences in responses between the two groups.

When the subjects were divided by age, seven were over 60 and six were under 25 years of age. The two groups had similar plasma lipoprotein-lipase concentrations at 16 and 24 hours after heparin (table 3).

Comparison of Two Doses of Heparin

Table 4 shows the plasma lipoprotein lipase found at 1, 4, 24, 36, 48, and 72 hours after the subcutaneous injection of 200 mg. of heparin in seven men. At 24 hours after heparin both glycerol production and optical density change indicated lipoprotein-lipase activity. This persisted to 36 hours. At 48 hours after heparin the values for both glycerol and optical density change were very low.

When the plasma lipoprotein lipase was compared at 24 hours for the two doses of heparin, 50 mg. and 200 mg., the resulting enzymatic activities were statistically alike (fig. 3). Although the larger dose had no conclusively greater effect at 24 hours, it did produce more lipoprotein lipase at 1 and 4 hours after injection. Comparative mean figures with regard to optical density change were:

	50 mg. (15 subjects)	*200 mg.* (7 subjects)
1 hour	0.273 ± 0.095 units	0.482 ± 0.059 units
4 hours	0.224 ± 0.097 units	0.429 ± 0.126 units

Lipoprotein-Lipase Response to Two Different Preparations of Heparin

Heparin (Upjohn) 100 mg. per ml. and heparin (Abbott), 400 mg. per ml. were given subcutaneously in doses of 200 mg. to the same seven subjects. One week separated the two experiments. The lipoprotein-lipase responses were identical at 4 and 24 hours after heparin. For example, the 24-hour values were as follows:

Heparin concentration (200 mg. dose)	Glycerol (μM per ml.)	Change in optical density (units)
100 mg. per ml.	0.21 ± 0.19	0.11 ± 0.09
	$p > 0.9$	$p > 0.9$
400 mg. per ml.	0.21 ± 0.13	0.11 ± 0.08

Thus these two different preparations, each in a different concentration, caused almost identical lipoprotein-lipase responses.

Lipoprotein Lipase after Prolonged Heparin Therapy

Eight patients with coronary or cerebral vascular disease who had been receiving 50 mg. of subcutaneous heparin daily for an average period of 12 months were tested for lipoprotein-lipase activity after a single 50-mg. injection of the drug. Despite the fact that these patients had not received heparin for a period of 36 hours before the test, they still had residual lipoprotein-lipase activity.

Table 2

*Lipoprotein-Lipase Response in Healthy and Atherosclerotic Subjects**

Hours after heparin (50 mg. subcutaneously)	Subjects†	Glycerol production (μM per ml.)		Optical density change (units)	
0	H	0.013 ± 0.015	$p > 0.4$	0.055 ± 0.038	$p > 0.2$
	A	0.024 ± 0.040		0.038 ± 0.026	
16	H	0.360 ± 0.082	$p > 0.3$	0.198 ± 0.076	$p > 0.9$
	A	0.310 ± 0.077		0.200 ± 0.059	
24	H	0.138 ± 0.079	$p = 0.6$	0.106 ± 0.056	$p > 0.7$
		0.169 ± 0.149		0.083 ± 0.047	

*Mean values are given.

†H = healthy subjects; A = atherosclerotic subjects.

Table 3

*Lipoprotein-Lipase Response in Young and Old Subjects**

Hours after heparin (50 mg. subcutaneously)	Subjects	Glycerol production (μM per ml.)		Optical density change (units)	
0	Young	0.010 ± 0.018	$p > 0.6$	0.043 ± 0.036	$p > 0.9$
	Old	0.023 ± 0.048		0.048 ± 0.041	
16	Young	0.360 ± 0.083	$p > 0.2$	0.198 ± 0.076	$p > 0.9$
	Old	0.293 ± 0.066		0.200 ± 0.060	
24	Young	0.110 ± 0.072	$p > 0.4$	0.091 ± 0.045	$p > 0.9$
	Old	0.145 ± 0.071		0.087 ± 0.048	

*Mean values are given for the six subjects under 25 years of age and for the seven subjects over 60.

Subsequently, the increase in plasma lipoprotein lipase at 8 and 12 hours was as great as or greater than for the group A subjects so tested who had not been receiving heparin daily (table 5). At 24 hours there were no net increases, but this fact must be considered in view of the lipoprotein-lipase activity already present at the zero-hour time in these men.

Anticoagulant Activity

The clotting time of whole blood was measured in all of the subjects at 1, 4, and 24 hours after the subcutaneous injection of 50 mg. of heparin. The mean increase of the clotting time after heparin was 39 per cent at 1 hour and 28 per cent at 4 hours. At 24 hours the clotting time had returned to the pre-heparin level. Thus 50 mg. of heparin had a mild, but detectable, anticoagulant effect.

Discussion

A significantly increased concentration of plasma lipoprotein lipase occurred for as long as 24 hours after the subcutaneous injection of 50 mg. of heparin. When the same dose was given intravenously, the duration of action was only one fourth as long. A similar duration of action for intravenous heparin has been found by others.[12] The 200-mg. dose of heparin given subcutaneously produced an initially greater quantity of lipoprotein lipase than 50 mg., but at 24 hours after injection, the lipoprotein-lipase responses after the two different doses were similar. The effects of the 200-mg. injection were dissipated almost completely 48 hours later.

Nikkila and Sirola[12] reported that 20,000 units of heparin (200 mg.) given subcutaneously produced a clearing activity in plasma for as long as 24 hours after injection. Engelberg[13] measured lipoprotein lipase after subcutaneous heparin in a dose of 200 mg. and found plasma lipolytic activity at 24 hours but little beyond this time.

Thus, the evidence suggests that, for the maintainance of significant plasma lipoprotein-lipase concentration on a long-term regimen, heparin should be given subcutaneously

Table 4

Plasma Lipoprotein Lipase after 200 mg. of Heparin Given by Subcutaneous Injection in Seven Subjects of Group B

Hours after heparin	Glycerol (μM per ml.) Mean	S.D.	p	Change in optical density (units) Mean	S.D.	p
0	0.029	0.024		0.028	0.018	
1				0.482	0.059	< 0.001
4				0.429	0.126	< 0.001
24	0.210	0.192	< 0.05	0.110	0.092	< 0.05
36				0.126	0.093	< 0.02
48	0.053	0.035	> 0.1	0.046	0.023	> 0.1
72	0.029	0.032	> 0.9	0.019	0.026	> 0.4

Table 5

*Lipoprotein-Lipase Response after the Long-term Daily Administration of Heparin**

Hours after heparin	Glycerol (μM per ml.) Mean	S.D.	p	Change in optical density (units) Mean	S.D.	p
0	0.069	0.125		0.073	0.053	
8	0.670	0.107	< 0.001	0.283	0.048	< 0.001
12	0.530	0.178	< 0.001	0.258	0.069	< 0.001
24	0.100	0.059	> 0.5	0.079	0.057	> 0.8

*The eight subjects recieved 50 mg. of heparin subcutaneously on the test day. The values after heparin were compared with the 0-hour values.

once a day. The dose of 50 mg. per day increased lipoprotein lipase in plasma for 24 hours and did not cause a profound anticoagulant effect. A 200-mg. dose given daily causes a therapeutic anticoagulant effect; with prolonged therapy the risk of bleeding might be great. A recent study emphasized the hazards in terms of thromboembolic episodes when heparin therapy was terminated abruptly.[14] These complications occurred 24 to 30 hours after the cessation of heparin therapy in patients with acute myocardial infarction. Such rebound phenomena might conceivably be expected from a regimen of intermittent subcutaneous injections of heparin.

As yet, the treatment of coronary atherosclerosis with heparin remains experimental. The use of heparin is advocated largely on the basis of its antilipemic effect. The most direct approach to a lessening of lipemia is dietary prudence; i.e., the avoidance of meals rich in fat and cholesterol. It is not known whether a combination of heparin therapy and dietary lipid restriction might be more effective than either therapy alone in ameliorating atheromatous disease.

Anticoagulant activity from a 50-mg. dose of heparin was present at 1 and 4 hours, but not at 24 hours after heparin. Such an in vitro finding at 24 hours does not necessarily indicate an absence of anticoagulant effect within the body. As Hartman and co-workers[15] have indicated, an anticoagulant effect from a given dose of heparin may be measured with more sensitive technics long after the whole-blood clotting time in glass tubes has become normal. It has also been suggested that a heparin-induced anticoagulant effect is measurable in interstitial fluid for a longer time than in blood.[16] Such studies provide additional evidence for the view that heparin continues to have an in vivo anticoagulant action after a return to normal of the whole-blood clotting time.

Our results support the information given by Baker[17] that the plasma lipoprotein lipase resulting 8 minutes after intravenous heparin was not affected by age or the presence of atherosclerosis. Sixteen and 24 hours after subcutaneous heparin, plasma lipoprotein lipase was similar in subjects under 25 and over 60 years of age. Nikkila and Niemi,[18]

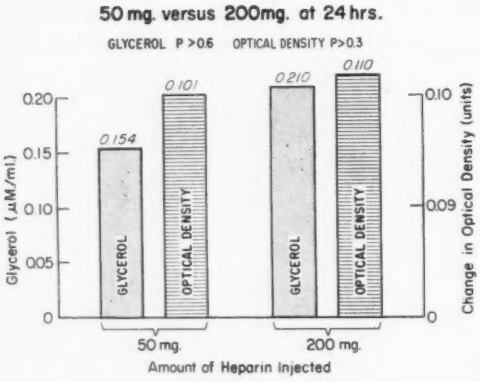

Figure 3

Comparison of the lipoprotein lipase response at 24 hours post-heparin between two different doses given subcutaneously. Group A subjects were given 50 mg. and group B subjects, 200 mg.

however, found more lipoprotein lipase in younger subjects after the injection of heparin intravenously. They measured only optical density changes; the means were 0.060 units for the younger and 0.023 for the older group. In our experience both of these optical density changes are slight. Our data were based upon optical density changes of the order of 0.200 for the older men and 0.198 for the younger.

Summary

Plasma lipoprotein lipase was measured at intervals after the subcutaneous injection of heparin in 34 men. This enzyme was significantly increased in plasma for as long as 24 hours after a 50-mg. dose. While the initial response was greater after a 200-mg. dose, the 24-hour lipoprotein lipase was similar for both 50 mg. and 200 mg.

Plasma lipoprotein lipase produced after intravenous heparin was dissipated after 6 hours.

The lipoprotein-lipase response at 16 and 24 hours after the subcutaneous injection of heparin was similar in men with coronary and cerebral atherosclerosis and in healthy men. Age did not affect plasma lipoprotein-lipase response.

Patients who had received 50 mg. of heparin subcutaneously each day for an average time of 12 months did not have exhaustion of the lipoprotein-lipase response to a test dose of heparin.

It is suggested that the daily administration of heparin is necessary to produce a continuous concentration of plasma lipoprotein lipase. A dose of 50 mg. (5,000 units) given subcutaneously produced a prolonged lipoprotein-lipase response and only a mild anticoagulant effect, unlikely to induce the complication of bleeding.

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When young men, not yet arrived at their full growth, are forcibly impressed into the military service, and thereby at once lose all hope of returning safe and sound to their beloved home and country, they become sad, silent, listless, solitary, musing, and full of sighs and moans, and finally quite regardless of, and indifferent to, all the cares and duties of life. From this state of mental disorder nothing can rouse them—neither argument, nor promises, nor the dread of punishment; and the body gradually pines and wastes away, under the pressure of ungratified desires, and with the preternatural sound of one side of the chest. This is the disease nostalgia. I have examined the bodies of many youths who have fallen victims to it, and have uniformly found the lungs firmly united to the pleura, and the lobes on that side where the obscure sound had existed callous, indurated, and more or less purulent. Some years ago this disease was very common, but is now rarely met with, since the wise arrangement has been adopted of limiting the period of military service to a certain number of years only.—From *On the Percussion of the Chest.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 132.

The Electrocardiogram, Vectorcardiogram, and Ventricular Gradient in the Tetralogy of Fallot

By N. P. DePasquale, M.D., and G. E. Burch, M.D.

THERE HAS BEEN increasing interest in the physiologic rather than the anatomic disturbances in tetralogy of Fallot.[1, 2] Accordingly, the degree of pulmonary stenosis and the size of the ventricular septal defect are the factors of physiologic importance in this congenital anomaly. The dextroposition of the aorta is functional due to the high ventricular septal defect, and the right ventricular hypertrophy is secondary to the pulmonary stenosis. Thus, tetralogy of Fallot embraces a spectrum of hemodynamic possibilities depending upon the relative degree of pulmonary stenosis and the size of the interventricular septal defect. At one extreme is the patient with complete pulmonary atresia and a large interventricular septal defect (pseudotruncus arteriosus) and, at the other, minimal pulmonary stenosis with a small interventricular septal defect. Between the extremes many physiologic possibilities exist, depending upon the relative severity of the two defects. There are, however, three distinct hemodynamic possibilities: (1) right-to-left intracardiac shunt at rest, (2) no right-to-left intracardiac shunt at rest but a right-to-left shunt upon exercise, and (3) a left-to-right intracardiac shunt but no right-to-left shunt either at rest or with exercise. In the first two instances a small left-to-right shunt may exist which is usually less than systemic blood flow. A fourth, exceedingly rare possibility exists which includes patients with pulmonary stenosis and interventricular septal defect but no intracardiac shunt either right-to-left or left-to-right at rest or upon exercise. Such a classification obviates such terms as acyanotic tetralogy of Fallot or "balanced tetralogy." The present study was undertaken to determine if the electrocardiogram and vectorcardiogram in tetralogy of Fallot reflect the physiologic variations described.

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Materials and Methods

The electrocardiograms of 140 patients with tetralogy of Fallot from the Charity Hospital of Louisiana in New Orleans were studied. The patients ranged in age from 2 months to 42 years, the mean being 8.2 years. Of the 140 patients 69 were male and 71 were female; 78, white, and 62, Negro. The diagnosis was made from clinical, roentgenologic, and laboratory data. All of the patients had arterial oxygen saturation determined at rest and upon exercise while breathing air and oxygen. Ninety-one patients had cardiac catheterization. Angiocardiography was performed in 32 patients. The diagnosis of tetralogy of Fallot was confirmed at autopsy in 26 patients.

Electrocardiograms were recorded within a few days of cardiac catheterization in all except three of the 91 patients catheterized. Spatial vectorcardiograms were recorded in 33 patients with use of the tetrahedral reference system as previously described.[3] The ventricular gradient of Wilson was calculated for all of the electrocardiograms,[4] which were enlarged four times by projection with an epidiascope in order to trace and measure the appropriate complexes. The normal values used in this study for $\hat{A}_{QRS}$ were $-21.5°$ to $104.9°$ and 3.1 to 40.6 μv. s. and for $\hat{G}$, $2.2°$ to $72.2°$ and 13.5 to 78.9 μv. s.[5]

The patients were divided into three groups according to the hemodynamic data, as already discussed: (1) right-to-left intracardiac shunt at rest, (2) right-to-left intracardiac shunt upon exercise only, and (3) no right-to-left intracardiac shunt but a left-to-right shunt. In this series of 140 patients with pulmonary stenosis and interventricular septal defect 107 patients were in group I, 14 patients in group II, and 19 patients in group III.

The patients in group I were all cyanotic at rest. The right ventricular pressure in all patients in whom cardiac catheterization was performed was essentially equal to the systemic arterial pressure. The mean right-to-left shunt equaled 46 per cent of the systemic venous return (table 1). The magnitude of the right-to-left shunt at rest varied over a wide range (15 to 90 per cent systemic venous return) as did the arterial blood

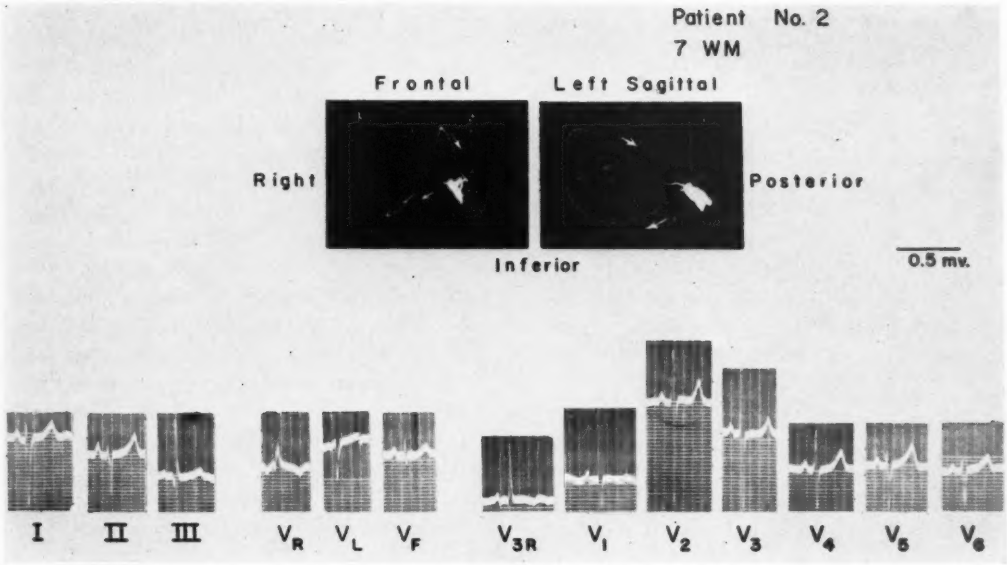

Figure 1

ECG and sVCG of a patient with classic tetralogy of Fallot (group I, type A).

oxygen saturation with the patient breathing oxygen at rest. Upon exercise there was frequently a precipitous decrease in the arterial blood oxygen saturation. The average arterial blood oxygen saturation while at rest breathing oxygen was 89 per cent, the value declining to 52 per cent with exercise. In some of the patients in group I a small left-to-right shunt existed at rest but disappeared with exercise in every instance. The magnitude of this shunt never exceeded systemic blood flow.

The patients included in group II were acyanotic at rest but developed a right-to-left shunt upon exercise. The right ventricular systolic pressure tended to be lower in these patients than in those of group I (table 1). Since the systemic arterial resistance must have equaled the resistance offered by the stenotic pulmonary valve at rest, there was no shunt across the interventricular septal defect. However, with exercise, increase in systemic venous return as well as the more forceful vigor of right ventricular contraction resulted in an increase in pulmonary arterial resistance so that a right-to-left shunt developed.

Group III included acyanotic patients who had a large left-to-right shunt but no right-to-left shunt either at rest or with exercise. In these patients the right ventricular systolic pressure was less than in those in groups I and II and lower than systemic arterial pressure (table 1). The gradient across the pulmonic valve was at least 35 mm. Hg in all of these patients. This gradient was considered to indicate organic stenosis. Patients with a gradient of less than 35 mm. Hg were considered to have interventricular septal defect with a functional pulmonary stenosis due to hypertrophy of the outflow tract and were not included in this study.

Results

The Electrocardiogram

Group I: Patients with Right-to-Left Intracardiac Shunt at Rest (107 Patients)

The electrocardiographic manifestations for group I patients are summarized in table 1 and figures 1 through 4.

The P Wave. The P-R interval was prolonged in only one patient. Right atrial enlargement was not a common finding in this group of patients. The P wave exceeded 2.3 mm. in lead II or III in 30 patients (28 per cent). A definite Q wave in the precordial leads recorded to the right of the transition zone, considered by some[6] to indicate right atrial enlargement, was present in 34 patients (32 per cent). In many patients the P wave appeared peaked or tent-shaped but it was not abnormally tall or wide. There was no disturbance in rhythm in any of the patients.

Table 1

Various Electrocardiographic Manifestations According to Group in the 140 Patients with Tetralogy of Fallot

Group	Number of patients	Mean RV pressure (mm. Hg)	Mean R→L shunt (% systemic venous return)	Mean L→R shunt PBF / SBF	A_{QRS} Direction (degrees)	A_{QRS} Magnitude (μV. s.)	A_T Direction (degrees)	A_T Magnitude (μV. s.)	Ĝ Direction (degrees)	Ĝ Magnitude (μV. s.)	Mean R/S in V_1	Abnormal R/S in V_1 (% patients)	Mean magnitude of Q_{III}	Q wave in III (% patients)	Q wave in V_5 (% patients)	Mean P-R interval (sec.)	Mean QRS duration (sec.)	Intrinsicoid deflection: Mean (sec.)	Intrinsicoid deflection: Delayed (% patients)
I	107	108	46	0.4	130	32.3	45	27.8	91	43.8	11.7	76	.88	75	13	.134	.080	.035	60
II	14	96	ex. only	1.5	107	34.9	48	42.7	69	62.5	11.8	86	.85	64	50	.142	.082	.042	78
III	19	83	—	3.5	90	29.9	64	32.5	75	57.0	3.2	66	.95	33	89	.146	.086	.031	33

The QRS Complex. The QRS complex was normal in duration in all patients. In two patients the QRS duration was 0.10 second, but there was no RSR′ pattern in lead V_1. The remainder had QRS durations between 0.04 and 0.09 second, the mean for the entire group being 0.08 second. Four types of QRS complexes were found in patients in group I.

Type A was the most common type of QRS pattern encountered (65 patients, 61 per cent) in patients of group I with tetralogy of Fallot (fig. 1). The R wave in lead I was extremely small and in some cases absent, whereas the S wave was deep but not abnormally wide. The magnitude of the S wave exceeded the magnitude of the R wave in all patients. The R wave was prominent in lead III, and the presence of an S wave in this lead was unusual. A Q wave was usually present in lead III (86 per cent). The R wave in V_1 was tall and the S wave small or absent. The intrinsicoid deflection in lead V_1 was late in 65 per cent of the patients and the R/S ratio was abnormally high in 67 per cent of the patients (mean ratio, 11.4). The Q wave was almost always absent in V_6 (94 per cent), whereas the R wave was small and the S wave large in magnitude but not wide. The R/S ratio in lead V_6 was less than unity in 85 per cent of the patients (mean ratio, 0.84).

Type B pattern of the QRS complex was found in 21 patients (20 per cent) of group I (fig. 2). The R wave in lead I was small but not as small as in type A, and the S wave was of large magnitude but not wide. The striking feature of the electrocardiograms from these patients was the extremely large magnitude of the Q wave in lead III. In some instances the area of this Q wave reached 5 μV. s. When the Q wave in lead III was of great magnitude, the R wave in lead I was more prominent. The precordial leads were essentially similar to those of type A.

Type C pattern of the QRS complex was found in 10 patients (9 per cent) of group I (fig. 3). The R wave in lead I was usually more prominent and the S wave less prominent than in types A and B. Lead III

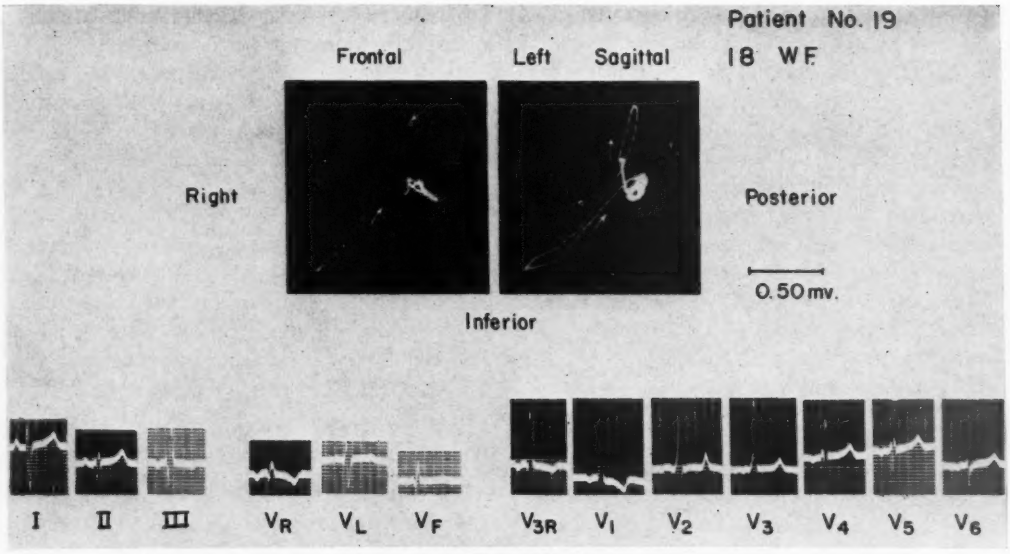

Figure 2

ECG and sVCG of a patient with classic tetralogy of Fallot with a Q wave of large magnitude in lead III (group I, type B). Note that in the sVCG there is a small deflection of the initial portion of the QRS sÊ-loop to the right and inferiorly resulting in an almost undetectable initial positive deflection in lead III. The QRS sÊ-loop is then projected sharply posteriorly, superiorly, and to the left resulting in an initial deep rS wave in lead III.

displayed a prominent R wave but rarely an S wave. A Q wave was usually present in this lead. There was an R and usually an S wave of large magnitude in lead V_1. The mean R/S ratio in lead V_1 was 8.5. The R wave in lead V_6 tended to be of greater magnitude than in types A and B, and the S wave was deep. The R/S ratio in lead V_6 was less than unity in 30 per cent of the patients (mean ratio, 1.2), whereas in types A and B the R/S ratio in lead V_6 was less than unity in 66 patients (62 per cent).

Type D pattern of the QRS complex was present in 11 patients (10 per cent) of group I (fig. 4). The R wave in lead I was usually prominent, equal to or exceeding the S wave in five of the 11 patients (45 per cent). A Q wave was usually present in lead III. The R wave in lead V_1 was of less magnitude than in the other types so that the R/S ratio was less in patients of type D than in any of the other types (mean ratio, 7.3). The R wave tended to be prominent in lead V_6 and the R/S ratio was greater than unity in all patients (mean ratio, 4.5).

The T Wave. The T wave in the 107 patients of group I tended to show little abnormality. The T wave was upright in standard leads I and II in almost all of the patients but was inverted in lead III in 31 patients (29 per cent) and diphasic or isoelectric in five patients (5 per cent). The T wave was inverted in V_1 in 61 patients (57 per cent), in V_2 in 20 patients (19 per cent), in V_4 in 10 patients (9 per cent) and in V_6 in seven patients (6 per cent).

Group II: Patients with Right-to-Left Shunt upon Exercise Only (14 Patients)

The electrocardiographic manifestations for group II patients are summarized in table 1 and figure 5.

The P Wave. The height of the P wave exceeded 2.3 mm. in four of the 14 patients (35 per cent), and a definite Q wave was

found in lead V_1 in three patients. The P-R interval was normal in all patients of group II. There were no rhythm disturbances in any of the patients.

The QRS Complex. One patient had a QRS interval of 0.10 second and an RSR′ complex in V_1. Another patient had classical complete right bundle-branch block. Based on the configuration of the QRS complex, two patients had patterns of type A, two of type B, and 10 of type D as discussed for group I (fig. 5). The R/S ratio in lead V_1 was abnormally high in 86 per cent of the patients (table 1). The R wave exceeded the S wave in magnitude in lead I in four patients (28 per cent) and the R/S ratio in V_6 was greater than unity in 71 per cent of the patients (mean ratio, 1.7).

The T Wave. Three patients (21 per cent) of group II had inverted T waves in lead I, and four patients (28 per cent) had inverted T waves in lead III. Eight patients (57 per cent) had inverted T waves in V_1; two (14 per cent) had inverted T waves in V_2; and one had inverted T waves in V_4 and V_6.

Group III: Patients without Right-to-Left Shunt Even with Exercise (19 Patients)

The electrocardiographic manifestations for group III are summarized in table 1 and figure 6. The electrocardiograms of this group of patients tended to display the patterns previously described for uncomplicated ventricular septal defect.[7]

The P Wave. The P wave did not exceed 2.3 mm. in height in any of the patients of group III. The P-R interval was prolonged in two patients. There were no disturbances in rhythm in any of the patients.

The QRS Complex. Six patients had electrocardiograms with "incomplete" right bundle-branch block (QRS interval, 0.10 second and RSR′ in lead V_1). The R wave in lead I was prominent and was of greater magnitude than the S wave in seven patients. An $S_1S_2S_3$ pattern (concordant S waves) (fig. 6*B*) was present in the standard leads in 45 per cent of the patients. A Q wave was present in lead III in 6 patients (33 per cent), and in lead V_6 in 16 patients (89 per cent) (table 1). The Q wave was of considerable magnitude in lead V_6 in four patients, a fairly frequent finding in uncomplicated ventricular septal defect.[7] The mean R/S ratio in lead V_1 was less in this group (mean ratio, 3.2) than in groups I and II (table 1). The R/S ratio in lead V_6 exceeded unity in all of the patients (mean ratio, 10.0) (fig. 6).

The T Wave. The T wave was negative in lead I in two patients and in lead III in three patients. The T wave was inverted in lead V_1 in 11 patients (58 per cent), in lead V_2 in three patients (16 per cent), and in leads V_4 and V_6 in one patient.

The Ventricular Gradient

The characteristics of $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ for the three groups of patients with tetralogy of Fallot are summarized in table 2 and figure 7.

Group I: Patients with Right-to-Left Intracardiac Shunt at Rest (107 Patients)

Before describing the $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ for the four electrocardiographic types encountered in this group, a general description of these parameters for group I is given.

The $\hat{A}_{QRS}$ was directed to the right and inferiorly or superiorly in the frontal plane in most of the patients. The majority of the vectors were located in the fourth and fifth sextants of the triaxial reference system. $\hat{A}_{QRS}$ was deviated more to the right than normal in 82 patients (77 per cent). The mean direction of $\hat{A}_{QRS}$ was 130° and the mean magnitude was 32.3 μv. s. (table 1, fig. 7).

The projection of $\hat{A}_T$ in the frontal plane was inferior and to the left in most of the patients. Occasionally it was directed to the left and superiorly. The mean direction of $\hat{A}_T$ was 45° in the frontal plane, the mean magnitude being 27.8 μv. s. (table 1, fig. 7).

The ventricular gradient ($\hat{G}$) was directed inferiorly and either vertically or to the right in most of the patients. The mean direction of $\hat{G}$ in the frontal plane was 91° and the mean magnitude was 43.8 μv. s. (table 1, fig. 7). The ventricular gradient was abnormal in magnitude or direction in 91 of the 107 patients (85 per cent). In 47 patients (44 per cent) the angle between $\hat{A}_{QRS}$ and $\hat{G}$ was

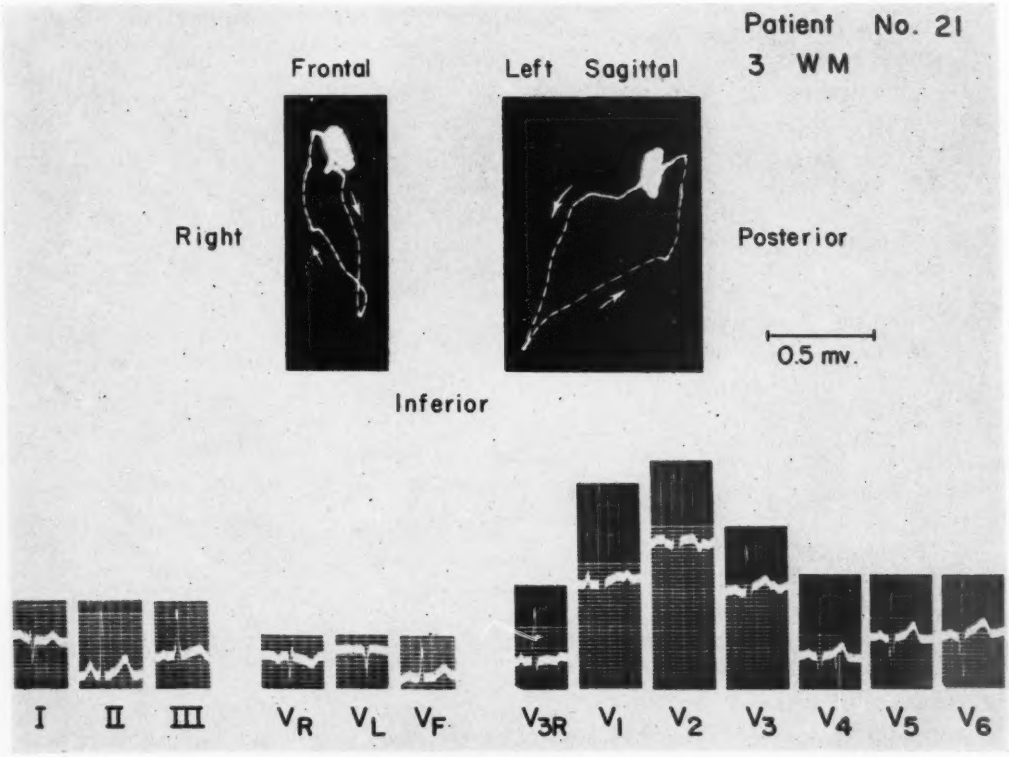

Figure 3

ECG and sVCG of a patient with tetralogy of Fallot with creased left ventricular electrical activity (group I, type C) as evidenced by an S wave of large magnitude in lead V_1, a taller R wave than usual in lead V_6, and a vertically directed QRS sÊ-loop.

abnormally large, and the angle between $\hat{G}$ and $\hat{A}_T$ was abnormally large in 67 patients (63 per cent) (table 2). $\hat{G}$ was directed more to the right than normal in 86 patients (80 per cent). In seven patients (6 per cent) $\hat{G}$ was abnormally large and in 11 patients (10 per cent) $\hat{G}$ was of less magnitude than normal.

In patients with type A electrocardiograms the $\hat{A}_{QRS}$ was deviated to the right and inferiorly with a mean direction of 134° and a mean magnitude of 33.4 μv. s. In 57 of the 65 patients (88 per cent) it was deviated to the right beyond the normal. The ventricular gradient ($\hat{G}$) was abnormal in all but five patients. The $\hat{G}$ was directed too far to the right in 60 of the patients (92 per cent), and the angles between $\hat{A}_{QRS}$ and $\hat{G}$ and $\hat{G}$ and $\hat{A}_T$ were abnormally wide in 48 per cent and 65 per cent of the patients, respectively. The mean direction of $\hat{G}$ in the frontal plane was 92° and the mean magnitude was 33.7 μv. s.

In patients with type B electrocardiograms the characteristics of the $\hat{A}_{QSR}$, $\hat{A}_T$, and $\hat{G}$ were similar to those described for type A. The mean direction of $\hat{A}_{QRS}$ in the frontal plane was 137° and the mean magnitude, 27.8 μv. s., whereas the mean direction of $\hat{G}$ was 91° and its mean magnitude 34.3 μv. s. The $\hat{A}_{QRS}$ was deviated more to the right than normal in 15 of the 21 patients (71 per cent). In 18 of the patients (86 per cent) $\hat{G}$ was directed more to the right than normal, and the angles between $\hat{A}_{QRS}$ and $\hat{G}$ and $\hat{G}$ and $\hat{A}_T$. were abnormally wide in 67 per cent and 76 per cent of the patients, respectively. Three

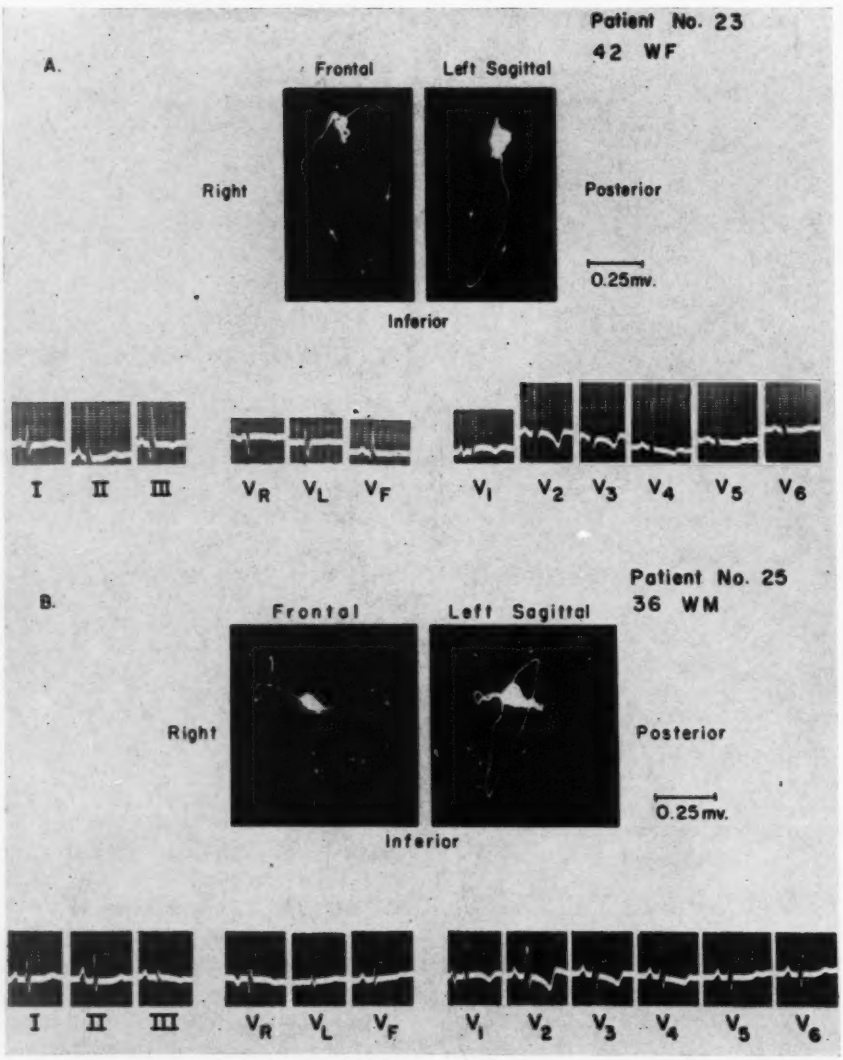

Figure 4

ECG and sVCG from two older patients with tetralogy of Fallot. The high R waves present in leads I, V_5, and V_6 of the electrocardiograms from these two patients were typical of the ECG from older patients with tetralogy of Fallot. The orientation of the QRS sÊ-loop to the left was also frequent.

of the 21 patients had normal ventricular gradients.

In patients with type C electrocardiograms the mean $\hat{A}_{QRS}$ was located at 119° in the frontal plane and the mean magnitude was 28.0 μv. s. The degree of rightward deviation of $\hat{A}_{QRS}$ was abnormal in six of the 10 patients (60 per cent). The ventricular gradient ($\hat{G}$) was projected inferiorly either vertically or slightly to the right in the frontal plane. The mean direction of $\hat{G}$ was 95° and the mean magnitude, 42.8 μv. s. $\hat{G}$ was deviated to the right beyond the normal in 4 patients (40 per cent). The angle between $\hat{A}_{QRS}$ and $\hat{G}$ was

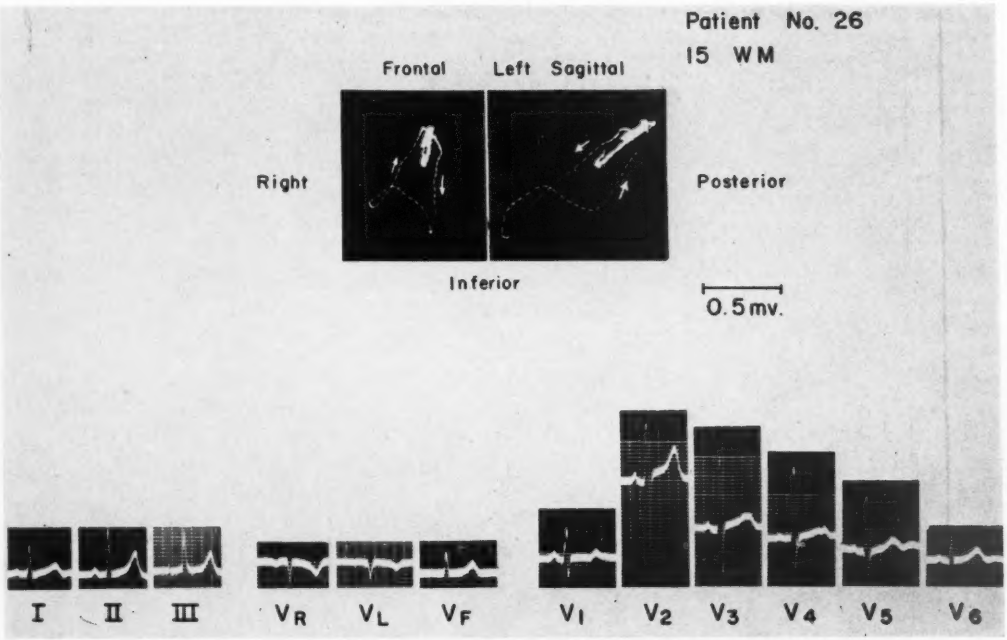

Figure 5

ECG and sVCG of a patient from group II with a right-to-left intracardiac shunt upon exercise only. Note the well-developed R waves in leads I, V_5, and V_6 and the moderately deep S wave in lead V_1.

abnormally wide in one patient, whereas the angle between $\hat{G}$ and $\hat{A}_T$ was abnormally wide in four patients. Two patients had a normal ventricular gradient.

In patients with Type D electrocardiograms $\hat{A}_{QRS}$ was projected inferiorly and to the left in five of the 11 patients. In the remaining patients it was oriented inferiorly and either vertically or toward the right. The mean $\hat{A}_{QRS}$ in the frontal plane was located at 91° and had a magnitude of 36.2 μv. s. In four patients (36 per cent) $\hat{A}_{QRS}$ was deviated more to the right than normal. The ventricular gradient ($\hat{G}$) was directed inferiorly and to the left in all except three of the patients. The mean direction of $\hat{G}$ in the frontal plane was 79° and the mean magnitude 52.8 μv. s. Six patients had normal ventricular gradients. The angle between $\hat{A}_{QRS}$ and $\hat{G}$ was abnormally wide in one patient, whereas the angle between $\hat{G}$ and $\hat{A}_T$ was abnormally wide in five patients.

Group II: Patients with Right-to-Left Shunt on Exercise Only (14 Patients)

$\hat{A}_{QRS}$ tended to be directed inferiorly and to the right in the frontal plane projection (fig. 7). The mean direction of $\hat{A}_{QRS}$ was 107° and the mean magnitude, 34.9 μv. s. $\hat{A}_{QRS}$ was deviated more to the right than normal in 11 patients and more to the left than normal in one patient.

$\hat{A}_T$ was fairly consistently oriented inferiorly and to the left in the frontal plane. The mean direction of $\hat{A}_T$ was 48° and the mean magnitude 42.7 μv. s. (fig. 7).

The ventricular gradient ($\hat{G}$) was projected inferiorly and to the left in the frontal plane, its mean direction and magnitude being 69° and 62.5 μv. s., respectively (fig. 7). In two patients the ventricular gradient was normal. In 11 patients $\hat{G}$ was deviated more to the right than normal and in one patient more to the left than normal. The angle between $\hat{A}_{QRS}$ and $\hat{G}$ was abnormally wide in seven pa-

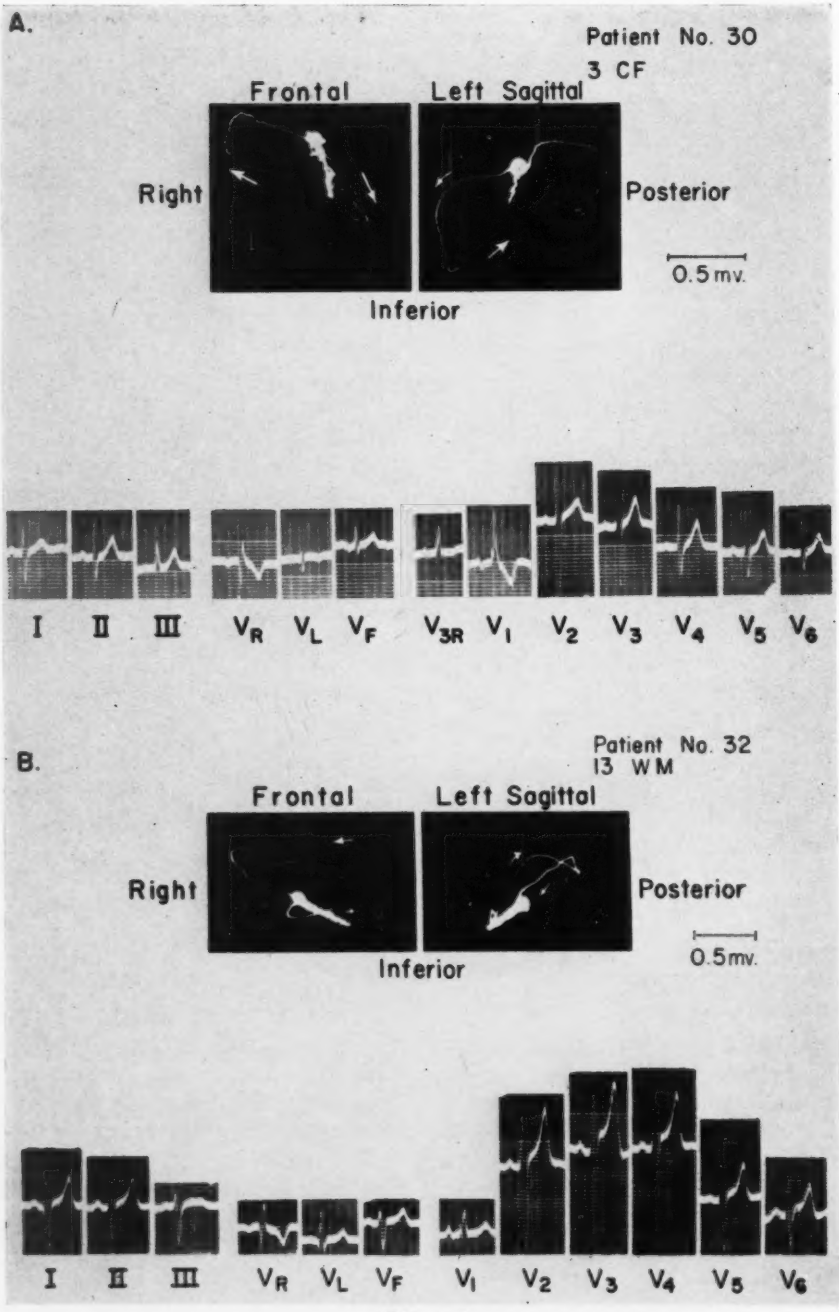

Figure 6

ECG and sVCG from two patients in group III. In patient no. 30 (A) there is a prominent R wave in leads I, V_5, and V_6 and a terminal projection in the sVCG. In patient no. 32 (B) note the $S_1S_2S_3$ pattern in the standard leads, the rSR' pattern in

Table 2

Relationship of $\hat{G}$ to $\hat{A}_{QRS}$ and to $\hat{A}_T$ in the Frontal Plane in the Three Groups of Patients with Tetralogy of Fallot

Group	Position of $\hat{A}_{QRS}$ relative to $\hat{G}$	Number of patients	$\hat{A}_{QRS}$-$\hat{G}$ 0-35	36-70	>70	Position of $\hat{A}_T$ relative to $\hat{G}$	Number of patients	$\hat{G}$-$\hat{A}_T$ 0-35	36-70	>70
I	Right	101	55	32	14	Right	6	2	—	4
	Left	6	5	1	—	Left	101	38	42	21
II	Right	12	6	4	2	Right	2	2	—	—
	Left	2	1	—	1	Left	12	6	6	—
III	Right	16	12	4	—	Right	16	15	1	—
	Left	3	3	—	—	Left	3	3	—	—

tients (50 per cent) and the angle between $\hat{G}$ and $\hat{A}_T$ was abnormally wide in six patients (43 per cent) (table 2).

Group III: Patients without Right-to-Left Shunt Even with Exercise (19 Patients)

$\hat{A}_{QRS}$ was directed inferiorly and to the left in 10 patients and either vertically or toward the right in nine patients. The mean $\hat{A}_{QRS}$ in the frontal plane projection was located at 90° and its magnitude was 29.9 μv. s. (fig. 7). $\hat{A}_{QRS}$ was located more to the right than normal in five patients (26 per cent).

$\hat{A}_T$ was located inferiorly and to the left in most of the patients. The mean direction of $\hat{A}_T$ in the frontal plane was 64°, the mean magnitude being 32.5 μv. s. (fig. 7).

The ventricular gradient was directed inferiorly and to the left in 16 patients and inferiorly and to the right in three patients. The mean direction of $\hat{G}$ in the frontal plane was 75° and the mean magnitude, 57.0 μv. s. (fig. 7). The $\hat{G}$ was deviated more to the right than normal in 11 patients. In four patients the angle between $\hat{A}_{QRS}$ and $\hat{G}$ was abnormally wide, whereas the angle between $\hat{G}$ and $\hat{A}_T$ was abnormally wide in one patient (table 2).

The Spatial Vectorcardiogram

Spatial vectorcardiograms (sVCG) were obtained for 33 of the 140 patients with tetralogy of Fallot. The results are summarized in figures 1-6 and 8.

Group I: Patients with Right-to-Left Intracardiac Shunt at Rest (25 Patients)

In all of the patients with type A electrocardiograms (17 patients), the maximal instantaneous vectors of the QRS sÊ-loops were directed inferiorly, to the right, and anteriorly. The mean direction of the QRS sÊ-loop in the frontal plane projection was 129° (range, 101° to 153°). In every instance the QRS sÊ-loop was inscribed in a clockwise direction in the frontal plane. The loops were generally wide, elliptical, and tended to display little if any distortion. In most of the patients the major portion of the QRS sÊ-loop was oriented to the right of the 90° axis. The anterior displacement of the QRS sÊ-loop in the left sagittal plane projection was marked in most of the sVCG (mean, 128°) (fig. 1). The maximal mean instantaneous vector of the T sÊ-loops was directed inferiorly, to the left, and anteriorly (fig. 8).

In types B and C (four patients) the QRS and T sÊ-loops were similar to those described for type A except that there tended to be less rightward orientation of the QRS sÊ-loop in the frontal plane projection (mean, 116°). As a result, a greater portion of the loop was oriented to the left of the 90° axis than in type A (fig. 3). There was also less anterior displacement of the QRS sÊ-loop in the left sagittal plane projection (mean, 115°) than for that in type A. One patient with type

lead V_1 and the equiphasic complexes (Katz-Wachtel) in leads V_2 through V_6. Also, there is a terminal projection in the sVCG directed superiorly, to the right, and posteriorly. The ECG and sVCG from these patients closely resemble those from patients with uncomplicated ventricular septal defect.

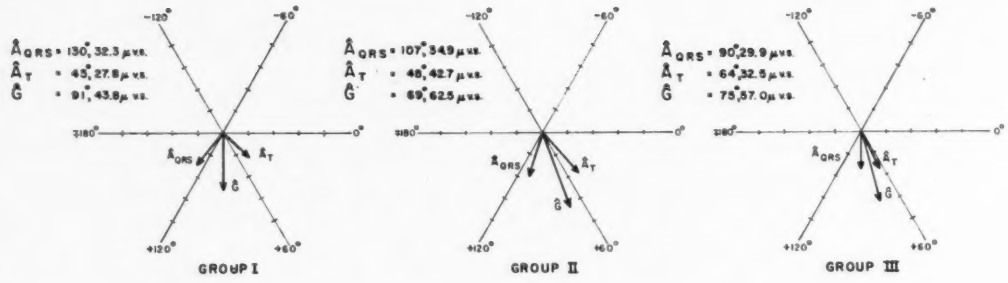

Figure 7

Mean $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ for the three groups of patients with tetralogy of Fallot.

B had a QRS sÊ-loop that was inscribed in a counterclockwise direction (fig. 2).

In three of the four patients with type D electrocardiograms, the maximal mean instantaneous vectors of the QRS sÊ-loops were directed inferiorly, to the left, and anteriorly (fig. 4). The fourth patient had a QRS sÊ-loop which was similar to that described for type A.

Group II: Patients with Right-to-Left Shunt on Exercise Only (Three Patients)

The maximal mean instantaneous vectors of the QRS sÊ-loops in the three patients in this group were directed inferiorly and vertically in the frontal plane projection with as much of the loop being oriented to the left of the 90° axis as to the right (figs. 5 and 8). The QRS sÊ-loop in the left sagittal plane projection was oriented anteriorly. All of the loops were inscribed in a clockwise direction.

In one of the patients the maximal mean instantaneous vector of the T sÊ-loop was directed to the right (fig. 8).

Group III: Patients without Right-to-Left Shunt Even with Exercise (Five Patients)

The maximal mean instantaneous vectors of the QRS sÊ-loops of this group of patients were directed inferiorly and to the left in the frontal plane projection (fig. 8). In four patients the loop was directed anteriorly and, in one patient, slightly posteriorly to the isopotential point. All but one of the loops rotated in a clockwise direction. In three patients a prominent terminal projection of the QRS sÊ-loop was directed to the right, posteriorly and superiorly to the isopotential point (fig. 6).

The maximal mean instantaneous vectors of the T sÊ-loops were directed inferiorly to the left, and in two patients were projected posteriorly and in one patient anteriorly to the isopotential point (fig. 8).

Discussion

Tetralogy of Fallot was considered in this discussion as a congenital cardiac defect in which the predominant lesions were pulmonary stenosis and ventricular septal defect. The three basic hemodynamic variants depend upon the relative degree of pulmonary stenosis and the size of the ventricular septal defect. In the patients with right-to-left shunt at rest the left ventricle receives only a portion of the total systemic venous return (as little as 20 to 30 per cent in severe defects). The "underloading" of the left ventricle results in hypoplasia of this chamber. Angiocardiographic studies have demonstrated that the lumen of the left ventricle is much smaller than that of the right ventricle,[8] and autopsy studies have repeatedly shown hypoplasia of the left ventricle. Brinton and Campbell,[9] in a necropsy study of 25 patients with tetralogy of Fallot, found that the right ventricle was generally 50 per cent thicker than the left ventricle. The anterior surface of

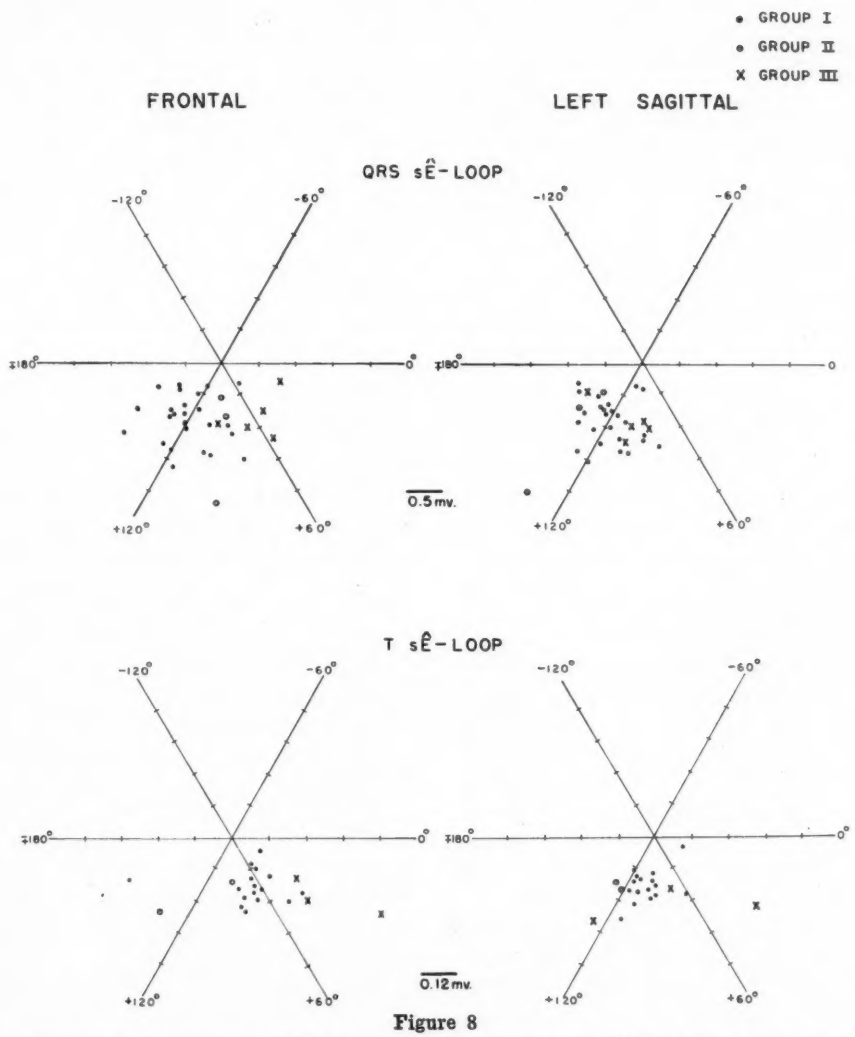

Figure 8

Location of the mean maximal instantaneous vectors of the QRS sÊ-loops and the T sÊ-loops in the frontal and left sagittal plane projections for the three groups of patients.

the heart is formed entirely by the right atrium and right ventricle, the left ventricle being displaced behind the right ventricle.[10] Owing to the hypoplasia of the left ventricle, the degree of clockwise rotation of the heart is probably greater in tetralogy of Fallot than in any other congenital cardiac defect. The apex of the heart, composed of the right ventricle, is lifted upward and forward.[11, 12]

The electrocardiograms from the patients with right-to-left shunt at rest reflect a marked degree of right ventricular hypertrophy as well as hypoplasia of the left ventricle and extreme clockwise rotation of the heart. Because of the presence of the interventricular septal defect, the highest level that the right ventricular pressure can reach is that of the arterial blood pressure. Therefore, in tetralogy of Fallot the right ventricular systolic pressure is usually between 95 and 125 mm. Hg.

The configuration of the QRS complex in V_1 is similar to that seen in pulmonary stenosis with a normal aortic root and right ventricular pressure in the range of 95 to 125 mm. Hg.[13] Clockwise rotation of the forward-lifted heart causes the early vectors of ventricular activation to be directed superiorly and to the left in the frontal plane. This results in a prominent Q wave in lead III and the absence of a Q wave in lead V_6. Because of the clockwise rotation of the heart and the hypoplasia of the left ventricle, an unusually small R wave is present in leads I, V_5, and V_6.

Certain aspects of the Q wave in lead III are of interest. According to Ziegler,[14] a Q wave in lead III is common in children and decreases in incidence with age. Weisbart and Simonson[15] found a prominent Q wave in lead III in 12 per cent of normal young men studied. These investigators measured the amplitude rather than the area of the Q wave. A report from this laboratory[16] of the electrocardiograms of 172 normal children from birth to 16 years of age, in which the area of the Q wave rather than its amplitude was measured, indicated that a Q wave was present in lead III in 61 per cent of the subjects studied and the mean area of the Q wave was 0.55 μv. s. $\pm$0.45 μv. s. No statistical relationship was found between the area of the Q wave in lead III and the patient's age. In the present study, a Q wave was found in lead III in 75 per cent of the patients in group I, and in 28 per cent of these patients it was two standard deviations or more from the mean for the normal children.

The absence of a Q wave in lead V_6 deserves comment. A Q wave is present in lead V_6 in well over 90 per cent of normal infants and children after the age of 1 month.[14] The youngest patient in the present series was 2 months old. The presence of a Q wave in lead V_6 in only 13 per cent of the patients in group I supports the idea that in tetralogy of Fallot there is marked clockwise rotation of the heart. Slightly more than half of the patients with uncomplicated pulmonary stenosis or pulmonary stenosis and interatrial shunt display a Q wave in lead V_6. Furthermore, when a Q wave is present in lead III, in these latter defects it rarely exceeds the normal limits for area.

The electrocardiograms (type D) of the older patients with tetralogy of Fallot tended to show more evidence of left ventricular activity electrically than did those of the younger patients. It is not known if this is due simply to the duration or physiologic mildness of the disease or if it is because only those patients who have a strong left ventricle survive into middle life.

$\bar{A}_{QRS}$, $\bar{A}_T$, and $\bar{G}$ in the patients with right-to-left shunts at rest had fairly uniform characteristics. $\bar{A}_{QRS}$ was directed inferiorly and toward the right (mean, 134°). In patients with uncomplicated pulmonary stenosis with right ventricular systolic pressures in the range of 95 to 125 mm. Hg, $\bar{A}_{QRS}$ tends to be located at 135° in the frontal plane projection.[13] Thus, it would appear that in the tetralogy of Fallot as well as in isolated pulmonary stenosis the location of $\bar{A}_{QRS}$ in the frontal plane depends at least to some extent upon the right ventricular pressure.

Since $\bar{A}_{QRS}$ and $\bar{G}$ were both deviated to the right, whereas $\bar{A}_T$ remained essentially normal in position, the angle between $\bar{G}$ and $\bar{A}_T$ was usually wider than that between $\bar{A}_{QRS}$ and $\bar{G}$. Because of clockwise rotation of the heart on its longitudinal axis, $\bar{A}_{QRS}$ was located to the right of $\bar{G}$ in most of the patients with right-to-left shunt at rest.

The mean $\bar{A}_{QRS}$ in the older patients (type D) was only slightly deviated toward the right and in five patients $\bar{A}_{QRS}$ was actually directed to the left in the frontal plane. These findings are considered further evidence of an increase in left ventricular muscle mass in these older patients. In fact, in five patients the ventricular gradient was normal, probably because of the balancing of electrical forces as the left ventricle hypertrophied.

The spatial vectorcardiograms (sVCG) described for patients with right-to-left shunt at rest were essentially similar in orientation, configuration, and rotation. Donoso et al.,[17] using a different method of electrode place-

ment have also noticed such consistency in the sVCG of patients with tetralogy of Fallot. The QRS sÊ-loop was oriented almost completely to the right of the 90° axis in the frontal plane. With this type of QRS sÊ-loop, an R wave of small magnitude and an S wave of great magnitude is expected in leads I and V_6 of the electrocardiogram. The marked anterior displacement of the QRS sÊ-loop in the left sagittal plane projection is probably a result of lifting of the apex of the heart, one of the characteristic anatomic alterations in the tetralogy of Fallot.

The small magnitude of many of the loops was at times striking, the maximal mean instantaneous vector of the QRS sÊ-loop in the frontal plane being less than 1 mv. in 60 per cent of the patients. This was presumably due to the hypoplasia of the left ventricle.

In the older patients with tetralogy of Fallot the QRS sÊ-loops were oriented inferiorly and to the left. The relatively greater degree of orientation of the QRS sÊ-loop to the left and the lack of anterior displacement of the loop in the older patients would seem to support the idea that with persistence of the anatomic defect there is increasing evidence of left ventricular electrical activity.

It is important to differentiate tetralogy of Fallot from pulmonary stenosis with reversed interatrial shunt. The sVCG of 10 patients with proved pulmonary stenosis and veno-arterial interatrial shunt have been studied in this laboratory. In six of these 10 patients the QRS sÊ-loop was oriented superiorly, to the right, and posteriorly in the frontal plane.[18] This spatial orientation of the QRS sÊ-loop was not encountered once in tetralogy of Fallot.

When the degree of pulmonary stenosis is less severe, fewer signs of marked right ventricular hypertrophy and extreme clockwise rotation of the heart are evident in the electrocardiogram. Those patients with right-to-left shunt on exercise only tended to have better developed R waves in leads I, V_5, and V_6 as well as deeper S waves in lead V_1 than those patients with right-to-left shunt at rest. In addition, a deep Q wave in lead III was less common and a Q wave in V_6 more common in the former group than in the latter.

The influence of the hemodynamic changes on the electrocardiogram in the patients with right-to-left shunt on exercise only deserves comment. Because of the left-to-right shunt at rest, and in spite of the presence of pulmonary stenosis, the pulmonary blood flow is increased. Therefore, the left ventricle is "overloaded" rather than "underloaded" so that it is not underdeveloped. With progression of the disease, some of these patients probably develop a veno-arterial shunt at rest. When a patient of this type becomes cyanotic, his electrocardiogram would be expected to be different from the type of electrocardiogram seen in the typical case of tetralogy of Fallot. In fact, Gasul and coworkers[19] have shown that patients with uncomplicated ventricular septal defects may with time develop infundibular pulmonary stenosis and arterial oxygen desaturation. $\hat{A}_{QRS}$ and $\hat{G}$ tended to be directed more to the left in the frontal plane than in the patients with right-to-left shunt at rest. Also, there was less tendency for the QRS sÊ-loop to be oriented to the right.

Patients who fail to develop right-to-left shunts even on exercise have only a mild degree of pulmonary stenosis. In this study a pressure gradient of greater than 35 mm. Hg across the infundibular zone or the pulmonary valve was accepted as evidence of an organic stenosis. This was based on the observations of Brotmacher and Campbell[20] in which the lowest pressure gradient across the pulmonary valve found in patients with confirmed pulmonary stenosis at autopsy was 35 mm. Hg. It is realized, however, that patients with functional pulmonary stenosis may occasionally have marked pressure gradients between the right ventricle and pulmonary artery. The electrocardiograms from patients with pulmonary stenosis and ventricular septal defect with left-to-right shunt only resemble those previously described for patients with uncomplicated interventricular septal defect. Since the ventricular septal defect with an

associated left-to-right shunt and not the pulmonary stenosis is the predominant disturbance, there is a tendency for hypertrophy of the crista supraventricularis to develop rather than hypertrophy of the right ventricle generally. The electrocardiograms of these patients often show incomplete right bundle-branch block and an $S_1S_2S_3$ pattern as well as a deep Q wave in lead V_6.[7] In these patients $\hat{A}_{QRS}$ was directed inferiorly and vertically in the frontal plane. In uncomplicated ventricular septal defect the mean $\hat{A}_{QRS}$ is directed toward the left.[7] This difference in the direction of $\hat{A}_{QRS}$ indicates that, although the patients in this group more closely resemble those with ventricular septal defect than those with tetralogy of Fallot, the presence of the mild pulmonary stenosis is sufficient to alter somewhat the orientation of $\hat{A}_{QRS}$ in the frontal plane. Again, it would seem that in patients with congenital heart disease the position of $\hat{A}_{QRS}$ in the frontal plane may reflect right ventricular pressure with some accuracy.

All of the patients without right-to-left shunts had QRS sÊ-loops that were oriented inferiorly and to the left. In the sVCG from three of these patients the centripetal limb of the QRS sÊ-loop was projected to the right, posteriorly and superiorly to the isopotential point. This type of terminal orientation of the QRS sÊ-loop was frequently found in uncomplicated ventricular septal defect and probably represents the late activation of a hypertrophied crista supraventricularis.[7]

From these data it may be postulated that in the tetralogy of Fallot the electrocardiogram, ventricular gradient and spatial vectorcardiogram vary with the degree of pulmonary stenosis in such a way as to display a progression from hypertrophy of the crista supraventricularis to generalized right ventricular hypertrophy with increasing degrees of pulmonary stenosis.

Summary

The electrocardiogram, ventricular gradient, and spatial vectorcardiogram were studied in 140 patients with proved tetralogy of Fallot. The patients were separated into three groups according to hemodynamic data.

The salient features of the electrocardiogram in patients of group I consisted of diminutive R waves in leads I and V_6, a deep Q wave and high R wave in lead III, a prominent R wave in lead V_1, which was not wide, and the absence of Q waves in leads I, V_L, and V_6.

The electrocardiogram in patients of group II was similar to that of the patients of group I except for the appearance of more signs of left ventricular electric activity and less clockwise rotation of the heart.

The electrocardiogram of the patients of group III was similar to that previously described for ventricular septal defect.

$\hat{A}_{QRS}$, $\hat{A}_T$, $\hat{G}$, and sVCG reflected the same general trend as the electrocardiograms.

The electrophysiologic data presented support clinical observations indicating that the tetralogy of Fallot includes patients with a wide range of hemodynamic differences.

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In submitting this to the public I doubt not that I shall be considered, by all those who can justly appreciate medical science, as having thereby rendered a grateful service to our art, inasmuch as it must be allowed to throw no small degree of light upon the obscurer diseases of the chest, of which a more perfect knowledge has hitherto been much wanted.

In drawing up my little work I have omitted many things that were doubtful and not sufficiently digested; to the due perfection of which it will be my endeavour henceforth to apply myself. To conclude, I have not been ambitious of ornament in my mode or style of writing, being contented if I shall be understood.—From *On Percussion of the Chest:* being a translation of Auenbrugger's original treatise, entitled, *Inventum Novum ex Percussione Thoracis Humani, ut Signo, Abstrusos Interni Pectoris Morbos Detegendi.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 124.

SPECIAL ARTICLE

The Role of Necrosis in the Origin of Electrocardiographic Alterations Characteristic of Myocardial Infarction

By M. G. UDELNOV

Action of Necrotic Tissue on the Intact Myocardium and the Method of Study

THE METHOD of monophasic or unipolar leads is used in all the diverse fields of electrophysiology: one electrode is placed on an altered section of the myocardium, nerve, or muscle. However, the reason for the registration of unipolar or monophasic waves by this method has yet to be explained. Injured tissue is a good physical conductor and therefore should, it seems, be in itself a continuance of the registering electrode and thus insure the registration of the action potential from the intact tissue, neighboring the altered region.

The injured tissue also does not have rectifier properties. It is therefore impossible to explain the "indifference" of the electrode placed on the injured tissue by the physiologic properties of the latter. We therefore decided to try to explain this phenomena of unipolar leads by the action of the necrotic tissue on the adjacent intact myocardial structures.

To study this problem in simple and easily controllable experimental conditions we decided against employing the usual method of forming a section of necrotic tissue by injuring the myocardial structures. Instead a strip of necrotic tissue was placed on the surface of the intact myocardium. This strip of tissue was originally taken from a skeletal muscle or from the ventricle and they were permanently injured beforehand. One of the registering electrodes was placed on the surface of this necrotic strip, now "glued" to the myocardium; the second electrode was placed on the surface of the atrium or ventricle (fig. 1).

We used this method for the following reasons: if the necrotic tissue of the altered region during the usual recording procedure produces unipolar recording by its action on neighboring intact structure then the foreign strip of necrotic tissue placed on the myocardium should also give a monophasic record in the electrocardiogram.

The very first experiments done on a frog heart in situ showed that the placing of necrotic tissue on the surface of the intact heart ventricle of a frog is accompanied by the appearance of monophasic waves (fig. 1): The monophasic tracing remains unchanged as long as the strip of necrotic tissue stays in contact with the myocardium. Control tests showed that the monophasic electrocardiograms recorded in these conditions were in amplitude, form, and duration very much the same as monophasic electrocardiograms recorded by the usual electrophysiologic method.

After the necrotic tissue was removed and the heart was washed with Ringer solution, a normal electrocardiogram was again recorded (fig. 1). Therefore, we may say that necrotic tissue has no permanent damaging effect on the myocardium.[1]

However, the functional changes in that part of the myocardium in contact with the necrotic tissue were very pronounced and disappeared only very slowly if the necrotic tissue was in contact with the myocardium for

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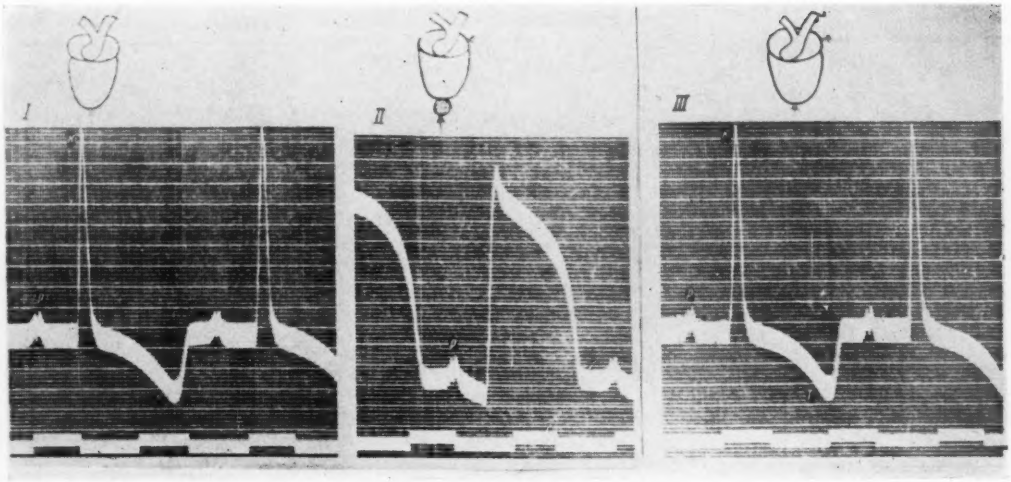

Figure 1

Electrographic alterations of a frog's heart when necrotic tissue is applied. Conditions of electrographic recording are schematically depicted above the record. I, normal electrogram; II, after the application of necrotic tissue to the apex of the ventricle; III, soon after the removal of the necrotic tissue. During application the electrogram is monophasic; after removal of the necrotic tissue, it is diphasic.

a few minutes. In such cases monophasic traits characterized by deviation of the RS-T segment and deformation of the T wave persisted for as much as 10 minutes after the necrotic tissue was removed.[2, 3] It is important to note that the monophasic electrocardiogram appeared only when the necrotic tissue was in contact with the myocardium. If the necrotic strip were placed under the recording electrode in the electric field of the heart, the electrocardiograms did not change. This phenomenon emphasizes that necrotic tissue in itself has no physical or chemical properties that would allow the electrode in contact with it to relay potential waves. We also observed that the necrotic tissue also produced a marked weakness of the ventricular contraction (fig. 2): the section of the myocardium under the necrotic tissue did not take part in the ventricular systole. It remained relaxed and bulged slightly during the systole. While the contracting part of the ventricle was of a pale color, this section remained dark red.

There was no systole in this section for quite a period after the necrotic tissue was removed. This fact, noted by Kyandjuntseva[2, 3] made possible the filming of these phenomena at high speed. Consecutive films (fig. 3) illustrate the development of the ventricular systole and the state of the myocardium at the apex in contact with necrotic tissue for a certain time. The bulging of the apex grows noticeably during the progressive development of the systole.

The area of the relaxed part of the myocardium is usually greater than the area of the necrotic strip. During the ventricular systole a small band of myocardial tissue lying close to the necrotic strip is also in a relaxed state.

No one can suppose that this section of the myocardium loses its property of excitation. Experiments with necrotic tissue placed on a section of the myocardium[4, 5] and on a spontaneously contracting trabecula of the atria,[7] which function as linear conductors of excitation, showed that the action of necrotic tissue blocks excitation.

The loss of excitation and its blockage by necrotic tissue was particularly noticeable when a strip of necrotic tissue was placed

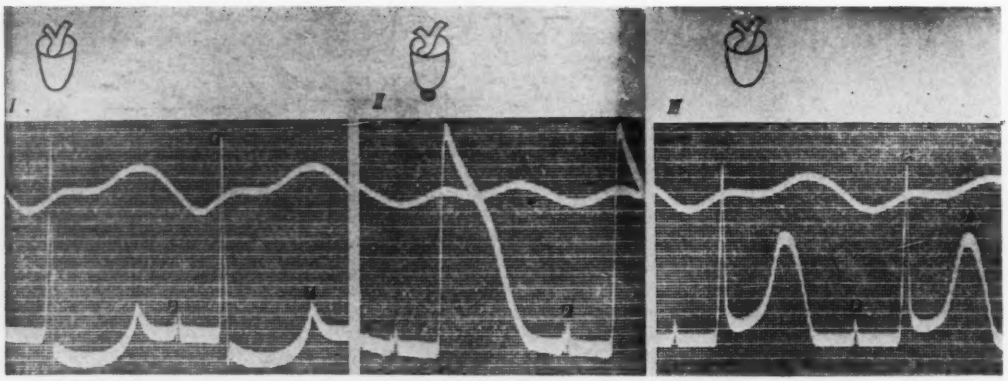

Figure 2

The alterations of a mechanogram (above) *and electrogram* (below) *of a frog's heart due to the application to it of necrotic tissue. The conditions of electrographic recording are schematically depicted above the records; I, normal electrogram; II, after application of necrotic tissue to the apex; III, after its removal. After the application of necrotic tissue to the heart's apex, the electrogram becomes monophasic while the contraction amplitude becomes smaller. These changes disappear after the necrotic tissue has been removed.*

on the bare atrioventricular funnel.[8] We call a section of the myocardium which has, under the action of necrotic tissue, lost its property of excitation a near necrotic zone (NNZ). The tissue of an NNZ does not take part in the general bioelectric activity of the heart. This fact may be proved by the appearance of a monophasic electrocardiogram of the ventricle in contact with necrotic tissue. Moreover, the action of necrotic tissue is accompanied by changes in the diastolic potential of the electrocardiogram.[6] The direction of this change (change of the demarcation potential) points to a marked depolarization of the myocardial sector acted upon by the necrotic tissue. The change of the diastolic level of the electrogram is approximately equal to half the amplitude of the monophasic electrogram. In certain cases the changes equaled two thirds of the amplitude of the monophasic electrogram but they were never greater.[6]

These experiments suggest that necrotic tissue not only depolarizes the neighboring myocardium but plays an active role in making it negative. Probably the depolarizing action of necrotic tissue is the cause for the loss of excitation and contraction of the myocardial elements forming the NNZ. The functional paralysis of the myocardium in the NNZ is not permanent.

As we have mentioned, the electrograms lose their monophasic quality and become normal shortly after the removal of the necrotic tissue.[1, 2, 6]

The no-systole state of the NNZ also disappears, while its excitability and contractibility become normal. The time for this is, however, far greater than the time of action of the necrotic tissue. It depends largely on the state of the heart and its muscles. Exhaustion, hypoxia, and poor blood supply lengthen this process. This restoration follows a normal and consecutive sequence.[5]

Figure 4 does not reflect all the possible dynamic variations of the restoration of the cardiac electrogram. It does, however, show the general scheme of this process and its most important features. A gradual deflation in the plateau of the monophasic electrogram reflects the appearance of an action potential of the tissue of the NNZ.

At the beginning the action potential has a small amplitude and is very short. Later the amplitude and duration of the action potential of the NNZ increase and then become

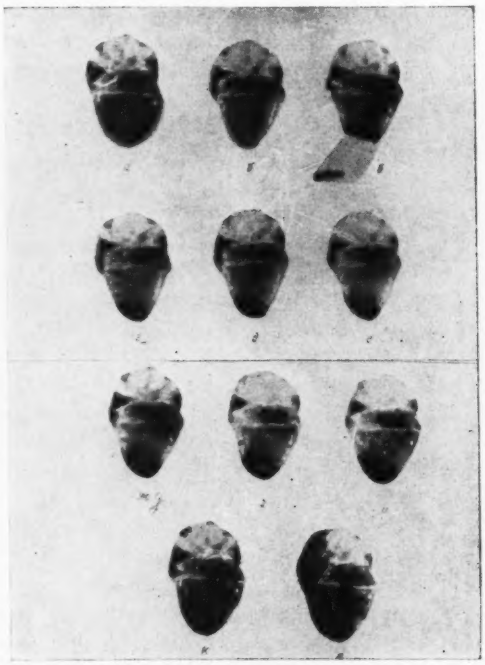

Figure 3

Functional changes in the myocardium under the effect of necrotic tissue. Photographs of a frog's active heart, taken at the speed of 8 to 10 frames per second. a, diastole of the intact heart; b, systole of the intact heart; c, systole of the heart during application of necrotic tissue; d, e, f, g, h, and i show that during systole the region in contact with necrotic tissue is relaxed. It bulges slightly toward the end of systole.

normal. At this time the RS-T segment reaches an isopotential level while the T wave regains its normal direction and form. The contractile properties of the myocardial NNZ are regained steadily and follow a definite law. After the necrotic tissue has been removed the myocardium does not contract and takes no part in several systoles. After a short period almost unnoticeable contractions may be seen in this area. These contractions begin with each new ventricular systole. These short contractions of the myocardial NNZ are followed by periods of relaxation, each of which takes place while the ventricular systole continues.

After some time the systole of the altered

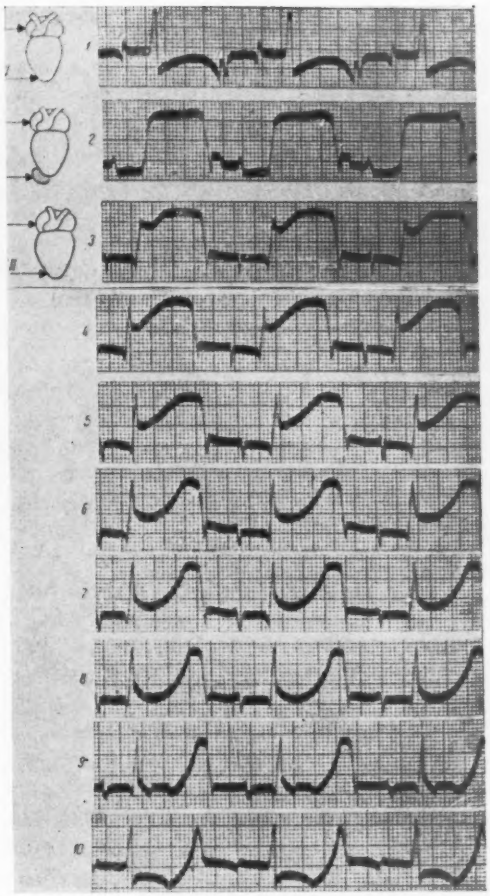

Figure 4

Electrographic alterations of a frog's heart after necrotic tissue has been removed from the myocardial surface. The situation of the recording electrodes is depicted on the scheme. 1, normal electrogram; 2, necrotic muscle is applied to the apex; 3, necrotic tissue is removed; 4-10, gradual renovation of the diphasic electrogram after necrotic tissue has been removed.

myocardial sector gradually becomes longer and longer until it becomes the same as the whole ventricular systole.

This recovery of the properties of the myocardial NNZ after the removal of necrotic tissue probably takes place by normalization processes in the ionic metabolism. The basis for such a statement will be shown in another part of this paper.

Inhibition of the Action of Necrotic Tissue on the Intact Myocardium

We began studying the internal mechanism of action of necrotic tissue on the myocardium by finding out if the effect of this action is due to the nature or type of injured tissue and to the method of necrosis.

Kyandjuntseva[2] tested the action of necrotic tissues on the myocardium with necrotic tissues from muscles, lungs, liver, stomach, skin, and blood clots taken from the living organism and from the ventricle of another animal.

All these tissues in which necrosis was produced by different methods, such as burning, ligatures of alimentary organs, etc., had the same action on the myocardium. They all paralyzed its functional properties with the gradual development of the NNZ and monophasic electrogram.

If the monophasic extent in the electrogram be used as an indicator of the depth of depression of the myocardial NNZ, then the area of this zone and the extent of functional depression of its tissue structures are seen to depend upon the extent of injury done to the tissue.

The skeletal muscle of a frog after 45 minutes of isolation may, when put in contact with the myocardium, cause typical monophasic traits of the electrogram, such as changes in the RS-T segment.

The similar action of necrotic tissues taken from different organs shows that they all have properties causing a functional depression of the myocardium. Control tests and experimental data show that this factor or property of necrotic tissues does not lie in the action of some substance such as "necrosive" (Menkin and other authors).

We did not forget about the very much higher concentration of intracellular potassium compared to the potassium in the tissue fluid and plasma, nor about the possibility of its leaking out in great amounts after tissue injury.[2, 4] Accordingly, we compared the action of necrotic tissue and potassium chloride on the myocardium and found them to be the same. Most important was the same depolarizing action of necrotic tissue and potassium chloride. Golovshchikov and Keder-Stepanova[9] similarly found the potassium ratio between the necrotic tissue and the myocardium to be important in the development of the necrotic tissue action.

Salmanovich[10] showed in frog and rabbit hearts that isolated muscle tissue depleted of most of its potassium also loses its property of paralyzing the myocardium. He also found that other ions and active substances in the necrotic tissue do not play any role in the mechanism of paralyzing the myocardium.

The potassium ions do not, however, fully explain the effect of necrotic tissue on the myocardium. The quick negative effect of necrotic tissue differs from the action of a 0.5 per cent solution of potassium chloride.[2] In the action of necrotic tissue the active movement of potassium is an important factor.

We also tested certain pharmacologic substances and physiologic effects that stop or limit parabiotical action of necrotic tissue on the myocardium. As was shown by Golovshchikov and Keder-Stepanova[9] atropine counteracts the effect of necrotic tissue on the myocardium, sharply limiting the area of the NNZ. We think that the effect of atropine is due to the stabilization of polarity of the cellular membranes. Atropine, also, slightly hyperpolarizes the membrane.

The paralytic action of necrotic tissue is limited to a great extent by the excitation of the vagus nerves.[11, 12] It was found[11] that the vagus nerves when inhibiting the heart cause a hyperpolarization not only in the physiologically normal heart tissues, but also in the NNZ. Not only that: in the depolarized tissues of the NNZ a slightly positive change in the resting potential may be noticed when compared to the growth of the demarcation potential in healthy tissues.

At the same time during vagus nerve action the NNZ grows smaller, while the heart electrogram and electrocardiogram become more normal.[11, 12]

Yastrebtseva et al.[13] showed that the irritation of the sympathetic nerves, on the con-

trary, increases the effect of necrotic tissue, perhaps because of the quicker and stronger heart beats.

Finally one must note that the depressing effect of necrotic tissue is probably universal; functional depression from necrotic tissue action takes place not only in heart tissues but equally in nerve structures. Yastrebtsova and Udelnov[14] pointed out that necrotic tissue in the frog brain (medulla) makes all reflex activity of this part of the brain impossible. Necrotic tissue on the vagosympathetic trunk blocks conduction.

Role of Necrotic Tissue on the Origin of Electrocardiographic Alterations Characterizing Focal Disease of the Myocardium (Infarction)

The foregoing experimental results suggest that a necrotic focus in the myocardium will always have a paralyzing action on the myocardial tissue adjoining it. This action should be accompanied by pathophysiologic alterations very much like those in the NNZ of the myocardium under the influence of necrotic tissue brought in from a foreign body. Accordingly we may assume that the method described in parts I and II may serve as an experimental model of certain pathophysiologic conditions that take place in the heart with the appearance of necrosis.

Since the electrocardiographic effect of necrotic tissue on the myocardium is much the same as the electrocardiographic alterations in cases of focal disease, we may again assume that this model permits reproductions of the electrocardiographic components of myocardial disease and thus helps solve the problem of its genesis.

Since necrotic tissue causes reversible alterations of the myocardial functional properties, we had in mind the reproduction of those electrocardiographic alterations that disappear during the recovery period when the normal electrocardiogram appears.

The problems formulated earlier were studied in experiments on frogs, cats, and rabbits in acute and chronic conditions.

The results of acute experiments[2] are illustrated by figures 5, 6, and 7.

The application of necrotic tissue is accompanied by the displacement of segment RS-T, alterations of T, and the first part of the ventricular complex (figs. 5 and 6). The degree of these alterations depends on the size of the necrotic tissue. By changing the size of the necrotic tissue we aimed at fixing the measurements of the smallest NNZ, which may be reflected in the electrocardiogram. We also assumed that the variation in size of necrotic tissue and the corresponding alterations of the electrocardiogram would make it possible to reproduce more or less accurately the electrocardiographic features corresponding to the different sizes of focal disease.

Electrocardiographic characteristics of focal disease of different localization were reproduced in the same way. Figure 6 illustrates alterations of the electrocardiogram of a cat, depending on the place of application of the necrotic tissue. The three standard leads are used. Discordant displacements of the RS-T segment are noticeable. When the necrotic tissue was placed on the left side surface closer to the atrioventricular boundary (the base of the left ventricle), the following changes occurred: an upward displacement of the RS-T segment while RS-$T_{2\text{-}3}$ move down, waves T_2 and T_3 are negative, and there are changes in the QRS complex.

The application of necrotic tissue to the apex of the ventricle causes contrary displacements of RS in leads I, II, and III. Sometimes a Q wave is markedly pronounced.

The application of necrotic tissue to the right ventricle closer to the base is accompanied by a downward displacement of interval RS-T while intervals RS-T_2 and RS-T_3 move upward. In certain cases a Q wave is very deep and pronounced, while waves S_2 and S_3 are larger than usual.

Figure 7 (tracing 2) illustrates the electrocardiographic alteration of a cat (with standard leads) after the necrotic tissue has been removed. Columns C, D, and E show the successive stages of recovery of the electrocardiogram after the removal of necrotic tissue. Recovery goes through the stage of a marked coronary T wave (C), the RS-T

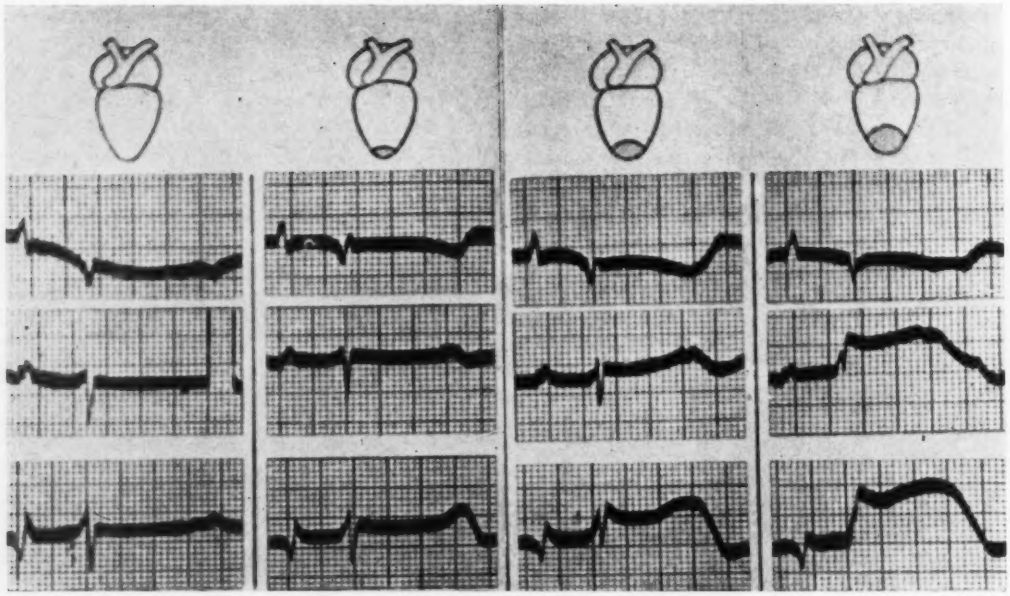

Figure 5

The dependence of the electrographic alterations of a frog's heart on the size of the necrotic tissue applied to the normal myocardium. First column. *The electrogram is normal.* Second column. *Electrocardiographic alterations when a piece of necrotic tissue measuring 2 mm.² is applied to the apex of the ventricle.* Third column. *The same, when the necrotic tissue measures 4 mm.²* Fourth column. *The same, when the necrotic tissue measures 8 mm.²*

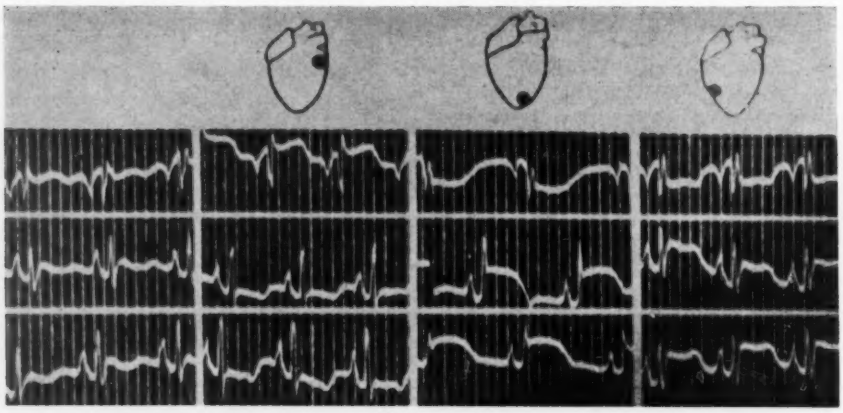

Figure 6

Electrocardiographic alterations of a cat depending upon the localization of necrotic tissue on the myocardium. First column. *Normal electrogram.* Second column. *Electrocardiogram after the application of necrotic tissue to the left-hand base of the ventricle.* Third column. *After the application of necrotic tissue to the apex.* Fourth column. *Application to the base of the right ventricle. The experiment was conducted on the same heart.*

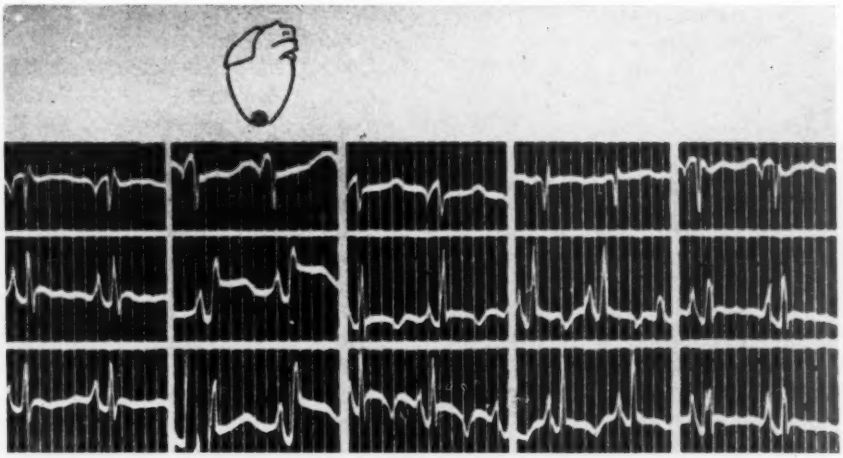

Figure 7

Electrocardiographic alterations of a cat when necrotic tissue is applied and after its removal. First column. *Normal electrocardiogram.* Second column. *Electrocardiogram recorded when necrotic tissue was applied to the apex of the heart.* Third column. *Electrocardiogram recorded 2 minutes after the injured tissue was removed from the myocardium.* Fourth column. *The same after 3 minutes.* Fifth column. *The same after 4 or 5 minutes.*

gradually returns to its normal level (D), and at last the negative T wave disappears (E).

Experiments have thus shown that alterations of the eletrocardiogram and their discordance, their dependence on the localization and size of the necrotic tissue in the area of the NNZ, are the same as those alterations that are characteristic of focal pathology in man.

The alterations in the electrocardiogram, noticeable after the removal of necrotic tissue, remind one to a certain point of the dynamic changes in the RS-T interval and T wave during the recovery period.

Alteration of Impulse Conduction in the Atrioventricular Area of the Heart under the Effect of Necrotic Tissue

Cases of depressed atrioventricular conduction accompanying necrotic foci has been described by Pardee, 1942; Katz, 1946; and Nezlin, 1951. In certain cases deep changes in atrioventricular conduction were not accompanied by pathologic symptoms of the conducting systems. This was shown by postmortem study of the heart.

The explanation of this fact usually is based on the assumption that together with the blocking of the blood stream in the damaged area ischemia of the conducting system occurs. Not only is this explanation completely a priori but it is hard to use in cases when the depressed atrioventricular conduction is combined with atrial infarction, and also with such depression of atrioventricular conduction for 10 or more days.

We thought it possible that such changes in atrioventricular conduction may depend on the influence of the necrotic area and involvement of the conducting system in the NNZ.

To check this assumption the necrotic tissue was placed on the bare conducting funnel of a frog spread out in the form of a plate, or on the surface of a cat's heart, lying next to the atrioventricular bundle. In this way a great variety of reversible forms of atrioventricular conduction defects can be seen, beginning with the syndrome of Wolff, Parkinson, and White, on through Wenkebach's periods and finishing in complete block.[8, 15] The results of these experiments done on the spread-Gramenitsky hearts of frogs are given

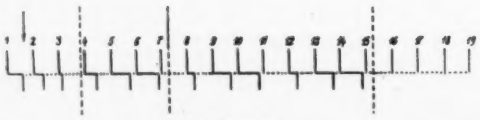

Figure 8

Consecutive stages of development of atrioventricular conduction disturbance resulting from the action of necrotic tissue on the conducting system. The arrow shows the moment of application of necrotic tissue. (Explanation in text.)

in figure 8. The alteration of atrioventricular conduction when necrotic tissue is placed on the epicardial surface near the atrioventricular bundle, is illustrated in figure 9 *A* and *B*.

We may conclude that reversible disturbances of atrioventricular conduction that take place during myocardial infarction of a definite locality may be due to the effect of the necrotic tissue in the damaged area and to the transformation of the conducting system into the NNZ.

Analysis of the QRS Complex Alterations, Characteristic of Myocardial Infarction

Our experimental model was further studied by Keder-Stepanova and Udelnov[16] in long-term animal experiments in which the electrocardiographic alterations after the placing of necrotic tissue on the intact myocardium were compared with blocking of the coronary arteries.

Fifty-eight rabbits were used. In 33 of them the alterations of the electrocardiogram were studied when necrotic tissue was applied to the intact ventricular myocardium under completely sterile conditions. Four rabbits composed the control group.

The comparison of the electrocardiographic alterations during the application of necrotic tissue to the base, middle, and top of the left ventricular frontal wall (12 rabbits) to the same during the blocking off of the anterior descending artery (9 rabbits) showed the following. In four, myocardial infarction measuring 1.5 cm.^{2} was found in the area of the base and middle of the frontal wall. In the five other cases myocardial infarction of approximately the same size covered the middle and anterior surface of the left ventricular apex. Experiments revealed that the character of alterations of the QRS complex were much alike in both cases, if these effects are approximately the same in their localization and the size of the inactivated myocardium.

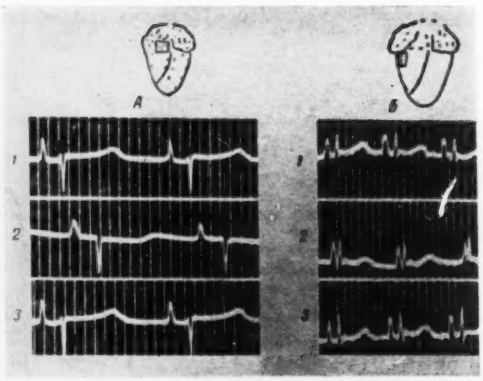

Figure 9

Alterations of atrioventricular conduction during the application of necrotic tissue to the epicardial surface of a cat's heart. A. *The electrogram of a 6-day-old kitten; lead II. 1. Normal; intervals: P-P, 0.62 second; P-R, 0.1 second, complex QRS, 0.017 second. 2. After the application of necrotic tissue to the region close to the coronary sinus (see schema). P-P, 0.65 second; P-R, 0.13 second; complex QRS, 0.03 second. 3. After the removal of necrotic tissue; P-P 0.63 second; P-R, 0.1 second; complex QRS, 0.017 second;* B. *Electrogram of a cat; lead II. 1. Normal electrogram; P-P, 0.4 second; P-R, 0.075 second; complex QRS, 0.04 second. 2. After the application of necrotic tissue to the lateral surface of the right ventricular base (see schema); P-P, 0.44 second; P-P, 0.04 second; complex QRS, 0.04 second. 3. After the removal of necrotic tissue; P-R, 0.75 second.*

However, important differences in the time needed for the development of the electrocardiographic alterations and the speed of electrocardiographic recovery were noted in cases of damage by the effect of necrotic tissue and by infarction due to ligature of arteries. In figure 10 the electrocardiograms of two such rabbits are compared. In one case the anterior descending artery was ligatured 2 or 3 cm. below the branching of the left coronary artery into the descending and the circumflex. Infarction due to the ligature

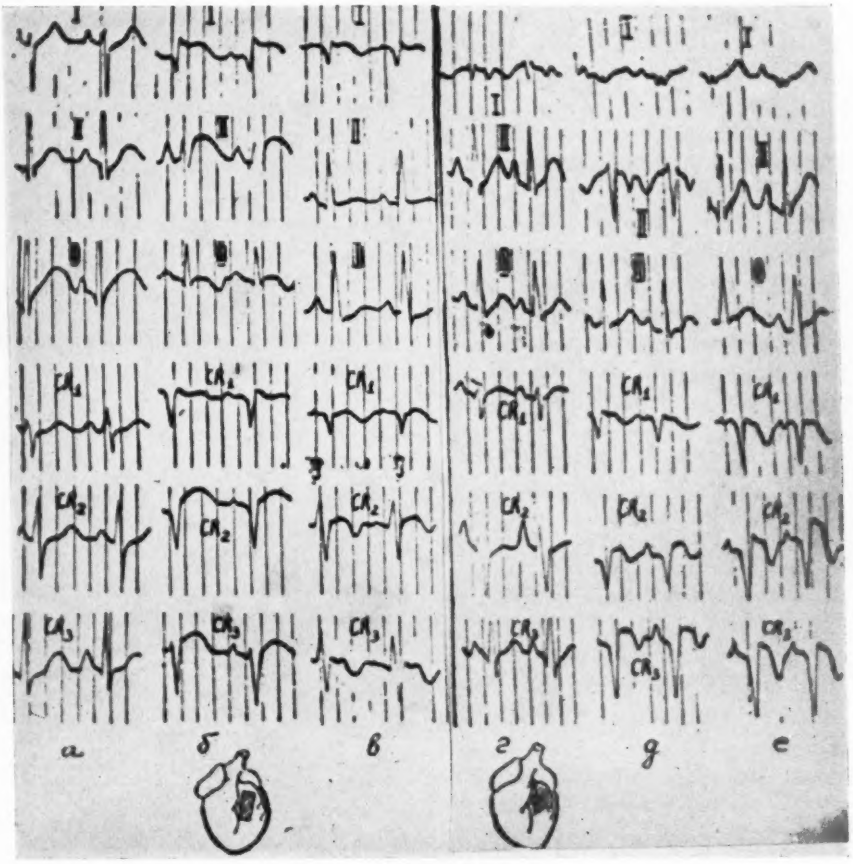

Figure 10

From the top to bottom in each tracing I, II, and III are standard leads, and CR_1, CR_2, and CR_3 are chest leads. a. *Rabbit electrocardiogram before necrosis and operation.* b. *Rabbit electrocardiogram immediately after necrotic tissue has been applied to the frontal wall of the left ventricle close to the interventricular septum, and the shutting off of the pericardium.* c. *Electrocardiogram of the same rabbit 18 hours after operation.* d. *Electrocardiogram of another rabbit immediately after ligation of the anterior descending artery and the shutting off of the pericardium.* e. *Electrocardiogram of the same rabbit 8 hours later.* f. *Electrocardiogram of the same rabbit 2 days later. The schema shows where the zone of damage is situated.*

developed, and when this rabbit was dissected 6 months later it was found that the myocardium was covered with cicatrices in the base and center of the left ventricular anterior wall. The electrocardiograms registered after the artery had been blocked are shown in the last three columns. In accordance with the localization and size of the infarcted area in this rabbit, a piece of necrotic tissue was placed on the heart of another rabbit (approximately 1.5 cm.^{2} and 1 mm. thick on the anterior wall of the left ventricle in the base and center region—closer to the interventricular septum).

The electrocardiogram of this rabbit before the application of necrotic tissue and after its application are shown in columns a, b, and c. The figure shows that, immediately after

necrotic tissue is applied and the pericardium is shut off, an alteration occurs in the QRST complex characteristic of an infarct in this location.

According to the localization of the "infarct" the chest leads are the most altered in this electrocardiogram, since they most clearly reflect damage in such locations. There also are alterations in the electrocardiograms of the standard leads.

In the other 26 rabbits we compared the alterations of the electrocardiogram that occurred when necrotic tissue was applied to the posterior lateral and posterior walls of the left ventricle, and when ligatures were placed on the corresponding arteries. (Ligatures were placed on different ramifications of the circumflex coronary artery and the posterior descending.)

The alterations of the complex were very much alike in both groups. At the same time there was a difference in the time needed for the development of alterations and for the normalization of the electrocardiogram. The electrocardiographic alterations after ligatures have been placed on arteries take place much later than the electrocardiographic effect of necrotic tissue. After the ligation of the circumflex branch of the left coronary artery (electrocardiograms were recorded every 30 minutes) it was found that only during the third hour after the operation sharp alterations of the electrocardiogram did appear. These differences in the time needed for the development of alterations are of great interest.

It appears that until necrosis develops the electrocardiogram shows no radical changes in the QRS complex, characteristic of myocardial infarction, even if the artery is occluded. Probably sudden and deep ischemia does not have an immediate effect on the alterations of the QRS complex. In other words, it does not cause these alterations independently from necrosis. The changes develop only after the tissue becomes necrotic. Together with this, electrocardiographic recovery appears earlier when under the effect of necrotic tissue than when the arteries are blocked by ligatures.

One may assume that the cause of this is the intensive circulation of cardiac lymph in the pericardial cavity, which relatively quickly begins to wash away the potassium of the necrotic tissue. However, the speedier recovery of the electrocardiogram in the case of necrotic tissue effect cannot serve as a basis for doubting the high activity of necrotic tissue as a factor changing the conditions of formation of electrocardiographic alterations.

Conclusion

This paper gives experimental data permitting us to suppose that electrocardiographic signs of myocardial infarction beginning at a definite stage of the disease, may be due to the paralyzing effect of necrotic focus on the surrounding myocardium.

Experimental modeling of certain stages of development of myocardial focal damage makes it possible to reproduce all the alterations of the electrocardiogram characteristic of myocardial infarction in the acute period as well as during the renovation periods (this is done by placing a piece of necrotic tissue on the intact myocardium).

The discordant alterations in the electrocardiogram are also reproduced together with displacements in the QRS complex (chest leads), which characterize a definite localization of the myocardial infarction. At the same time, the experimental model copying the effect of a necrotic focus on the intact myocardium allowed us to find important supplementary pathophysiologic characteristics of the heart in cases of myocardial damages.

It was found that the necrotic focus due to ischemia or other factors causes by its effect functional paralysis of that myocardial region, which surrounds the contact of necrotic tissue and is much larger in size.

This myocardial region, which we have called the near-necrotic zone (NNZ), does not take part in the general systole of the heart and is excluded from the summary bioelectric activity of the myocardium.

Depending upon the localization of the focus of damage and, accordingly, depending upon what structures of the heart are included in the NNZ, either the contracting myocardium or main structures of the conducting system are reversibly paralyzed.

The consequence of such different localization of the focus of damage may be depression of the contracting functions of the heart or the reversible depression of excitation and conduction. According to this hypothesis, different reversible depressions of atrioventricular conduction were reproduced with the help of the mentioned experimental model. These reversible changes are typical of myocardial infarction with a definite localization.

The experiments of different scientists, cited in this paper, revealed that the tissue of the NNZ is depolarized and, accordingly, is electro-negative in respect to the normal myocardium. The depolarization of structures is the direct cause of functional depression of the myocardium in the NNZ.

Experiments have shown that necrotic tissue causes a depolarizing and depressing effect on the surrounding structures of healthy myocardial tissue by means of potassium ions. After injury the cellular structures cannot retain their intercellular potassium. Potassium, flowing out after the cell's injury, has a depolarizing effect on the myocardium of the NNZ.

The presence of this depolarized NNZ, excluded from all bioelectric activity in one sphere of leads, is the condition responsible for "unipolar" leads and the monophasic electrogram of the heart.

The region of necrosis and the NNZ must have a certain minimum size so as to ensure the "indifference" of the registering electrode placed on it.

This condition also determines the monophasic symptoms (displacement of segment RS-T) and the alterations in the ventricular complex in the electrocardiogram recorded in standard and chest leads.

Experiments showed that nervous effects, the conditions of blood flow, and certain other factors may change the size and length of the NNZ.

The depth of functional alterations of structures in the NNZ may also be changed.

However, wide compensating possibilities of the organism such as nervotrophic effects and adaptive changes in the coronary blood flow, as was shown in our experiments on mammals, may bring about changes but cannot exclude the appearance of the NNZ as a consequence of the direct influence of necrotic tissue on the myocardium.

The effect of necrotic tissue may, up to a point, be limited by the action of atropine.

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The following corollaries are the result of my observations of inflammatory diseases of the chest, studied under the sign of morbid resonance:

1. The duller the sound, and the more nearly approaching that of a fleshy limb stricken, the more severe is the disease.

2. The more extensive the space over which the morbid sound is perceived, the more certain is the danger from the disease.—From *On Percussion of the Chest.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 130.

CLINICAL PROGRESS

A Guide to Anticoagulant Therapy

By BENJAMIN ALEXANDER, M.D., AND STANFORD WESSLER, M.D.

THIS ARTICLE* has been prepared to provide guiding principles and practical recommendations for the proper use of anticoagulant drugs. No consideration has been given to the indications for therapy or to the merits of the various agents in the prophylaxis or treatment of specific diseases. Also, fibrinolytic agents alone, or in conjunction with anticoagulant therapy have not been included because sufficient clinical experience has not yet been accumulated to permit recommendations concerning their use. This article, therefore, has been designed to assist the physician who has already decided to invoke treatment.

Initial Screening

It is assumed that a complete history, physical examination, and certain minimal laboratory studies will be performed on any patient for whom anticoagulant therapy is considered. Since hemorrhage is the greatest hazard even in well-controlled therapy, a careful search for actual or potential causes of bleeding must precede the administration of these drugs.

The hemostatic mechanism constitutes one of the lifesaving homeostatic functions. If it fails, one incurs the risk of serious disability or death from hemorrhage. Not only should one know whether a patient is actively bleeding at the time he is seen, but also whether the patient has ever had excessive bleeding whenever he has been hurt, cut, or subjected to other trauma. A history of repeated or episodic bleeding is crucial in alerting the physician to the possibility that his patient is a bleeder. Several specific questions are helpful in this regard: Are there bleeders in the family? Has the patient had frequent nosebleeds? Do his gums bleed on brushing the teeth? Has the patient experienced unusual hemorrhage following dental extraction? Is there easy bruising manifest by ecchymoses without apparent injury? Is there excessive menstrual flow, or has there been excessive hemorrhage after childbirth? Are there bleeding hemorrhoids, or other sites from which the patient has bled from time to time? Does bleeding stop promptly after cuts and scratches? Is there a history of severe hemorrhage after surgical procedures, such as tonsillectomy? A "no" to all these questions readily excludes hemorrhagic disorders in the vast preponderance of individuals.

In addition to the recognition of a bleeding diathesis, a good history can suggest dietary defects leading to hemorrhage, such as lack of vitamin C, or evidence of prior overt bleeding such as from peptic ulceration, esophageal varices, colitis, polyps, or past ocular or intracranial hemorrhage. The history may also reveal significant information concerning hypertensive, hepatic, and renal disease, each of which may be associated with hemorrhage, as well as the likelihood of major surgery in the immediate future. Finally, careful questioning will yield information concerning

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Supported by research grants H-656 and H-1027, National Institutes of Health, and by a grant-in-aid from the American Heart Association.

*To be published as a booklet for the American Heart Association.

Table 1

Synonymy of Blood Clotting Factors

Factor*	Other names	Clotting phase
I	Fibrinogen	Third, fourth
II	Prothrombin	Second
III	Thromboplastin	Second
IV	Calcium	First, second, ? third
V	Ac-globulin, labile factor, proaccelerin, accelerator factor, plasma prothrombin converting factor	First, second
VII	Proconvertin → convertin, stable factor, serum prothrombin conversion accelerator (SPCA), prothrombinogen, autoprothrombin I, ? prothrombokinase	Second
VIII	Antihemophilic factor (AHF), Antihemophilic globulin (AHG), Hemophilic factor A, platelet cofactor I, thromboplastinogen, thrombocytolysin	First
IX	Plasma thromboplastin component (PTC), Christmas factor, hemophilic factor B, autoprothrombin II	First
X	Stuart factor, Stuart Prower factor	First, second
Profibrinolysin	Plasminogen	Fourth
Fibrinolysin	Plasmin	Fourth
Hageman factor	HF	First
Plasma thromboplastin antecedent	PTA Hemophilic factor C	First

*Nomenclature of clotting factors, designated by Roman numerals, is in accordance with recommendations of the International Committee on Nomenclature of Blood Clotting Factors.

chronic medication, such as steroids, that may predispose to hemorrhage.

On physical examination acute massive bleeding may be recognized by the signs of shock or by the local painful accumulation of fluid in a joint, muscle, or retroperitoneal areas, often with associated fever. Pallor, ecchymoses, adenopathy, or hepatosplenomegaly may suggest a disorder possibly associated with hemostatic defects. If the blood pressure cuff is allowed to remain inflated half way between systolic and diastolic pressure for 5 minutes, abnormal fragility of the capillaries (Rumpel-Leede test) may be revealed.

Minimal laboratory procedures should include a hemoglobin determination, a blood smear to establish the presence of an adequate number of platelets, a urinalysis, and a stool examination for gross and occult blood.

This initial screening is simple and requires little additional time. The recognition of hemorrhage or a tendency to bleed, however, does not constitute a blanket contraindication to anticoagulant therapy. Clinical judgment is required at all times to balance the anticipated hazards of hemorrhage against the threat of thromboembolic disease.

Hemostatic Mechanism

An understanding of the coagulation sequence is necessary to the proper use of anticoagulant drugs. The most recent schema is divided into four phases (tables 1 and 2). The intravascular fluidity of blood is believed to be dependent upon a delicately balanced state in which procoagulant forces are counteracted by anticoagulant forces. Under certain circumstances, this equilibrium may be disturbed, resulting either in overt clinical bleeding, on the one hand, or excessive thrombus formation, on the other.

Hemostasis depends, however, not only on

the fibrin clotting system and on the quantitative and qualitative aspects of platelet function, but also on the integrity of the vascular tree, especially in the microcirculation. While blood clotting factors affected by anticoagulant agents are fundamental in hemostasis, equally important, and too often disregarded, are the noncoagulation aspects of the hemostatic mechanism, both in the screening of patients and as a cause of hemorrhagic complications attending therapy. In some instances, malfunction of mechanisms other than coagulation, e.g., vascular, may explain hemorrhagic phenomena occasionally encountered, even when clotting factors have been maintained at so-called "therapeutic levels." The physician should be particularly alert to this possibility in those disorders known to be associated with hemorrhage on a vascular basis, namely, hypertension, diabetes, nutritional inadequacy, vasculitis, congenital malformations, infection, allergic and anaphylactic disorders, and polycythemia. Finally, certain occupations predisposing to trauma may present special hazards in individuals receiving anticoagulant therapy.

Anticoagulant Agents

The two most widely used agents are heparin ("direct" anticoagulant) and the coumarin derivatives and related compounds ("indirect" anticoagulants). Their use requires comprehension of their physiologic effects and of the numerous variables influencing their action, as well as familiarity with the guides to administration, contraindications, and appropriate antidotes. *The drug response for a given patient may vary even from day to day, as a consequence of numerous physiologic factors as well as pathologic processes. Accordingly, treatment must be individualized.*

Heparin

Heparin exists in the various tissues of the body, particularly the liver and lung, and most likely in the mast-cell granules. Following its discovery in 1916 by McLean and Howell, many properties of this naturally occurring sulfated mucopolysaccharide have been elucidated, and its general clinical usefulness has been thoroughly investigated since it was first employed as an anticoagulant by Murray and by Crafoord. The effectiveness of synthetic congeners (heparinoids) has been explored, but it is generally accepted that their toxic side-reactions make them undesirable except perhaps in rare instances where the natural heparins cannot be used.

Action

The anticoagulant action of heparin, attributed to its highly negative charge, depends upon its inhibition of certain interactions involved in thromboplastin elaboration, in thrombin formation, and in thrombin disposition (table 2). The latter effect occurs either by enhancement of the thrombin inhibitory action of the natural plasma antithrombin, or by another as yet obscure thrombin inhibitory mechanism. In appropriate doses, heparin also prevents platelet agglutination and, in addtion, is said to potentiate the fibrinolytic system.

Other biologic effects of heparin include its lipemia-clearing action, its enhancement of vascular permeability, its blockade of the local and generalized Shwartzman and Arthus phenomena, its inhibition of trypsin and hyaluronidase, its inactivation of serotonin and certain snake venoms, and its increase in the I^{-131} triiodothyronine uptake of red blood cells.

Even in large doses heparin has no effect on blood pressure (except in rare instances), peripheral or coronary circulation, respiration, body temperature, renal and hepatic function, blood chemistry, or red and white blood cells.

Absorption, Fate, and Administration

Within 15 minutes after the intravenous injection of heparin, 30 per cent is found in the liver, where it is inactivated by heparinase. Within 30 minutes, 2 per cent, and within 24 hours, 40 per cent, appears in the urine—largely as a breakdown product, "uroheparin." Excretion occurs via both glomeruli and tubules, and the amount thus eliminated is substantially reduced by renal

Table 2

*Current Coagulation Scheme**

Phase I: Formation of thromboplastic activity

IA: Elaboration of intrinsic thromboplastic activity

(1) Hageman "complex" $\xrightarrow[\text{surface}]{\text{"foreign"}}$ active Hageman factor (HF)

(2) HF + plasma thromboplastin antecedent (PTA) + factor IV (Ca^{++}) → (HF + PTA) "complex"

(3) (HF + PTA) "complex" + factor IX (plasma thromboplastin component —PTC) + IV → active IX

(4) IX + factor VIII (antihemophilic factor —AHF) + factor X (Stuart) + IV → intermediate product I

(5) Intermediate product I — platelet "factor 3" + IV → intermediate product II

(6) Intermediate product II + factor V (Ac-globulin) + IV → "intrinsic" thromboplastin ("intrinsic prothrombinase")

1B: Elaboration of extrinsic thromboplastic activity

(1) Tissue $\xrightarrow{\text{"Injury"}}$ factor III (tissue thromboplastin)

(2) III + VII (proconvertin) + IV → active factor VII (convertin)

(3) VII + V + X + IV → "extrinsic" thromboplastin ("extrinsic prothrombinase")

Phase II: Formation of thrombin from factor II (prothrombin)

IIA: Intrinsic system

"Intrinsic" thromboplastin + II + IV → thrombin

IIB: Extrinsic system

"Extrinsic" thromboplastin + II + IV → thrombin

Phase III: Formation of fibrin from factor I (fibrinogen)

Thrombin + I → fibrin + → fibrinopeptide
Thrombin + Antithrombin → metathrombin

Phase IV: Dissolution of fibrin by fibrinolysin (plasmin)

(1) Activator + profibrinolysin (plasminogen) → fibrinolysin (plasmin)

↑

Blood kinase
Tissue kinase
Urokinase
Streptokinase

(2) Fibrinolysin + Fibrin → lysed fibrin
+ I → destroyed fibrinogen
+ Antifibrinolysin (antiplasin) → destroyed fibrinolysin

*Nomenclature of clotting factors, designated by Roman numerals, is in accordance with recommendations of the International Committee on Nomenclature of Blood Clotting Factors (table 1).

Not included in the scheme are all the known, or postulated, inhibitors, or any negative feed-back mechanisms. In the formulation of the equations no consideration is given to whether the components are involved stoichiometrically or enzymatically.

Heparin inhibits "intrinsic" thromboplastin formation and also inhibits the action of thrombin. Coumarin-type compounds depress factors II, VII, IX, and X.

injury. The importance of both liver and kidney function in the disposal of heparin warrants caution in its use when disease of these organs is present. Heparin, in contrast to coumarin drugs, does not pass the placental barrier, and does not appear in milk.

One milligram of the crystalline standard heparin-sodium salt is equivalent to 100 U.S.P. units or 130 international units. The specific activity of highly purified material from different species varies widely, depending on the molecular chain length.

Administered in the form of a soluble salt, heparin is best given intravenously, preferably intermittently, but also by continuous infusion. The subcutaneous and intramuscular routes have also been used. By mouth, sublingually, or applied dermally the agent has little, if any, effect.

The anticoagulant action is proportional to the dose, varies from patient to patient, and becomes evident within minutes following intravenous administration. The over-all result is retarded coagulation manifested by the elevated *clotting time* of freshly shed blood. *This is the cardinal laboratory guide to dosage.* The bleeding time, which reflects more the response of the microvascular tree to trauma, is unaffected.

The anticoagulant effect of heparin is short lived; for example, 50 mg. may prolong the clotting time for 2 to 4 hours following intravenous administration. Peak prolongation occurs within minutes after injection, after which the clotting time gradually returns to normal. Coagulation is less retarded when heparin is given by intramuscular or subcutaneous routes, and the duration of the effect, although more prolonged, is not infrequently erratic. This prolonged effect following intramuscular and subcutaneous administration is a disadvantage when one wishes to shift from heparin to a coumarin compound, because sustained elevated blood levels of heparin interfere with the prothrombin time determination, as well as with the reversal of its anticoagulant effect with protamine, should this be necessary.

Toxicity

Heparin is essentially nontoxic. Rarely, alopecia may occur. In certain individuals the drug may cause untoward reactions, which range from mild urticaria to sudden, severe hypotension, respiratory distress, and chest pain. Most rarely, transient thrombocytopenia has been observed shortly after its administration. Heparin does not interfere significantly with the extravascular deposition of fibrin, and hence does not retard the healing of surgical wounds.

Antidotes

The anticoagulant action can be promptly reversed, milligram for milligram, by an equivalent amount of protamine sulfate. This markedly basic protein has a strong affinity for heparin, thus combining with it to give a relatively insoluble product. Protamine is therefore extremely useful as an antidote. Protamine is available in 1 per cent solution in 5-ml. vials. It is slowly administered intravenously after dilution in physiologic saline, in an amount equivalent to the last dose of heparin but never in excess of 50 mg. Its antiheparin effect lasts about 2 hours. Some heparin activity may reappear, if the anticoagulant was administered in large doses shortly before it was deemed necessary to reverse its action. *Blood or plasma transfusions, although of value in replacing blood lost from hemorrhage, are not specific antidotes against heparin, as they are against the coumarin drugs.*

Coumarin Derivatives and Related Compounds

Since the discovery by Link and Campbell over 20 years ago of bishydroxycoumarin (Dicumarol) and its relation to hemorrhagic spoiled sweet clover disease of cattle, significant advances have been made in the basic and therapeutic aspects of this and related substances, termed "indirect anticoagulants." Following the first therapeutic use of bishydroxycoumarin by Meyer and Bingham, and Butt and Allen, more than 100 chemically related compounds have been studied, but only a small number are generally accepted as reasonably safe agents (table 3).

Action

There is considerable agreement that all these agents depress the identical specific plasma clotting constituents concerned with the formation of thrombin from prothrombin (table 2). In contrast to heparin, they have no direct action on coagulation in vitro. Generally referred to as "prothrombinopenic" drugs, they lead after a variable latent period to a reduction in plasma factors II (prothrombin), VII (proconvertin), IX (plasma thromboplastin component), and X (Stu-

Table 3

Properties of Some Coumarin-Type Compounds

Class	Generic name	Trade name	Usual initial doses (mg.)	Usual maintenance doses (mg.)	Usual onset of peak activity (days)
Coumarin					
	Bishydroxycoumarin	Dicumarol	300–600	25–100	1.5–3
	Ethyl biscoumacetate	Tromeran	1500–2400	600–900	1–2
	Cyclocumarol	Cumopyran Cumopyrin	100–200	15–40	1–2
	Acenocoumarol	Sintrom	10–20	3–5	1–2
	Pheonprocoumon	Liquemar Marcoumar Marcumar	20–40	3–5	1–2
	Warfarin	Athrombin-K Coumadin Pan Warfarin	40–60	5–10	1–2
Indandione					
	Phenindione	Athrombin Bindan Danilone Dindevan Dineval Indema Indon PID Pindione	200–400	50–100	1–2
	Diphenadione	Dipaxin	20–50	3–5	1–2
	Anisindione	Miradon	500–700	50–150	1–2

art). By thus retarding and limiting the rate and amount of thrombin formation, clotting is slowed.

There is no universal agreement concerning the sequential order in which the specific factors become decreased. It is generally accepted, however, that factors VII and X decline before prothrombin. Observed variations in the onset of factor IX depression (frequently the last to be so affected) may be related to the use of different drugs, dosage schedule, and assay technics. Although the anticoagulant effect was initially attributed to diminution of plasma prothrombin per se, it now appears that depression of the other factors is at least equally important.

Coumarin-type compounds also decrease platelet adhesiveness, depress the activity of several platelet enzymes, and alter the fibrinolytic system. Other biologic actions include increased capillary permeability, increased coronary blood flow, increased red cell uptake of radioactive thyroxin, interference with oxidative phosphorylation, and increased urinary uric acid excretion.

Presumably all these agents act on the liver, where they are fixed, metabolized, and degraded at variable rates, followed by excretion through the renal and biliary tracts. Although the precise mechanism by which the "prothrombinopenic" effect is induced is obscure, it is likely that synthesis of the clotting factors is inhibited. This effect is in equilibrium with the patient's stores of vitamin K_1, a nutrient obtained from intestinal bacterial synthesis as well as by ingestion of vitamin K_1—containing foods such as mature grains, spinach, cauliflower, cabbage, and tomatoes. The coumarin drugs, resembling the vitamin in chemical structure, are thought to compete as an antimetabolite with the vitamin, for the apoenzyme functioning in the synthesis of the pertinent clotting factors.

Absorption, Fate, and Administration

Important in the use of these drugs is consideration of the various factors that influence the individual reaction to a given dose. For example, bishydroxycoumarin, the earliest agent used, and the one concerning which most knowledge has been accumulated, is

relatively insoluble, is more slowly absorbed, is bound longer in the plasma, remains for more prolonged periods in the liver, and is degraded there more slowly than some of the other related compounds. Accordingly, its "prothrombinopenic" effect is slow in appearance, more retarded in reaching peak activity, more cumulative, and more slowly dissipated. At the other extreme is warfarin, which is very soluble, and indeed is the only agent that can be given intravenously, intramuscularly, and rectally, as well as by mouth. This may be particularly advantageous, for example, when for any reason oral intake is temporarily precluded during the course of therapy.

The solubility characteristics that affect absorption and transfer to the liver also bear on the question of whether a particular drug should be administered in single or multiple daily doses. Thus, it is believed by some that the more soluble agents such as ethyl biscoumacetate, warfarin, and indandione derivatives should be given in divided doses for optimal sustained effect.

The variables inherent in a given individual are to a great extent responsible for the difficulties in maintaining the prothrombic activity at the desired level during therapy. Their importance, however, cannot be overemphasized. These varying influences may be physiologic or may arise as a consequence of disease. Clearly the net effect of a given drug dose will depend somewhat on the initial stores of the pertinent clotting factors in both the circulation and extravascular depots and their rates of mobilization, as well as upon their rates of synthesis and turnover. The latter are measured in terms of hours in contrast to other plasma proteins, such as albumin with a half life of approximately 3 weeks. Accordingly, the momentary effect of an agent that only partially blocks synthesis of a factor that is being rapidly consumed, is subject to wide variations. On this basis alone fluctuation may be anticipated from day to day in a given individual.

Although the initial depressing effect of a single priming dose is fairly uniform for each compound, wide variations occur in the total duration of the effect among different individuals, and in a given subject from time to time. It should be noted that debilitated and cachectic individuals are very sensitive to these drugs. Variation in a given individual is also observed during the course of maintenance therapy. This has been attributed to fluctuations in gastrointestinal, hepatic, renal, and metabolic functions secondary to physiologic or pathologic disturbances. The physician should therefore be alert to possible changes in the state of these organs, particularly during long-term therapy. Other pathologic states also influence the reaction to these drugs; for example, individuals with fever or scurvy are said to manifest increased sensitivity to the coumarin-type agents.

Also, there is considerable experimental evidence indicating that the prothrombinopenic effects of the coumarin congeners, as measured by the prothrombin time and hemorrhagic tendency, are enhanced by stressful stimuli and adrenocortical hormones.

Mention has been made of the antagonistic relationship between vitamin K_1 and the "prothrombinopenic" drugs. The patient's nutritional state with regard to this fat-soluble vitamin will therefore influence considerably the degree of "prothrombinopenia" induced. Body stores of the vitamin, initial or periodically supplemented from intake, can influence the ebb and flow of the pertinent factors dependent on this nutrient for synthesis. Here again, the nature of the diet, hepatic function, gastrointestinal motility, and fat absorption as well as intestinal bacterial flora (which may be greatly influenced by antibiotics), will exert their effects.

Chemical methods for measuring many of the "prothrombinopenic" agents in the plasma are available. This may be valuable in those instances where obscure hypoprothrombinemia and bleeding are suspected to be a result of self-induced medication. Also useful in this regard is the fact that if a suspect chemical is administered to a test animal and

a hypoprothrombinemic state ensues, this constitutes strong evidence of the coumarin nature of the material, since few if any other agents give this biologic reaction.

Some properties of the many available coumarin-type anticoagulants are listed in table 3. Measurement of the speed of the conversion of prothrombin to thrombin in a plasma sample is used as the guiding laboratory procedure for measuring their anticoagulant effect at any given time. Since it is not known which, if any, of the affected clotting components are paramount in the development of thrombosis, on the one hand, or of hemostatic failure during therapy, on the other, the practical laboratory tests most widely used are those that reflect the overall effects on clotting kinetics rather than a procedure that measures any single factor.

Although some anticoagulant effect of the "prothrombinopenic" agents is demonstrable within 24 hours after administration, peak activity may not be obtained until some time thereafter, depending upon the properties of the particular drug employed, the priming dose, and the metabolic processes described above.

Patients are occasionally encountered who are inexplicably resistant or sensitive to coumarin-type drugs. In addition, subjects have been observed who, after being steadily and satisfactorily maintained on a given drug for a long interval of time, will develop hemorrhagic phenomena coincident with a marked drop in prothrombic activity, especially during acute infections.

It may be summarily stated, especially in view of the many variables involved, *that the physician must treat each patient on an individual basis. If he is not prepared to do this, he should not administer anticoagulants.*

Toxicity

As with heparin, toxic reactions (aside from bleeding) to the coumarin-type drugs are rare. Nausea, vomiting, diarrhea, and leukopenia are sometimes observed. More serious, but nonetheless unusual, are hepatic and renal damage, fever, rash, jaundice, leukemoid reactions, and thrombocytopenia. The skin eruption, generally appearing prior to the other manifestations, may permit early recognition of toxicity and prompt shift to another drug. The untoward hematologic reactions are more frequent with the indandiones than with the coumarins. Of all the coumarin-type compounds, bishydroxycoumarin is least toxic.

One additional point regarding the indandiones is worthy of note. Following the first day of therapy the urine may be colored orange-red, attributed to a metabolic breakdown of the drug. It can be avoided by a large intake of water, or by diluting and acidifying the urine to pH 4.2. No toxic phenomena are associated with the excretion of the pigment although albuminuria is not uncommon during the first few days of therapy. This soon disappears, despite continued use of the drug.

Although not a "toxic" effect, coumarin-type compounds pass the placental barrier, and also appear in milk. For these reasons, they are considered to be contraindicated in pregnancy or in the puerperium. Although the small amount of drug that may be ingested by the normal lactating baby is not likely to compromise hemostasis despite the physiologic hypoprothrombinemia and decrease in factors VII, IX, and X in the immediate neonatal period, it can have dire consequences in premature infants.

Antidotes

Vitamin K_1 is effective in reversing excessive anticoagulant action. Administered intravenously, subcutaneously, intramuscularly, or by mouth—in this order of preference for attaining most rapid anticoumarin effect—some correction is demonstrable within a few hours, and full correction is usually attained within 24 hours.* Water soluble derivatives are distinctly less effective in this regard than the natural vitamin. It should be noted that *large* doses of vitamin K_1 may make the patient subsequently resistant to the coumarin drugs for several

*For dosage see pages 134 and 135.

weeks, should resumption of therapy be necessary. Although vitamin K_1 correction of drug-induced "prothrombinopenia" is fairly prompt, immediate reversal of the clotting defect can be attained by transfusion with blood, plasma, or plasma fractions* rich in the pertinent clotting factors. Because the involved factors are relatively stable, ordinary ACD banked blood, bank plasma, or lyophilized plasma are fully potent and will exert their effects almost immediately. Three units of blood or plasma should generally suffice, while the simultaneously administered vitamin K_1 will set in motion the regeneration of the respective clotting factors. In patients with limited cardiac reserve such volumes may be hazardous unless blood loss has been significant.

Contraindications to Anticoagulant Therapy

In general, anticoagulants should not be employed under the following circumstances: a hemorrhagic diathesis, severe hypertension, cerebrovascular hemorrhage, active ulceration or overt bleeding from the gastrointestinal, respiratory, genitourinary or pulmonary tracts,† surgery of the central nervous system, inadequate laboratory facilities, and inadequate cooperation of the patient with the therapeutic regimen. In pregnancy the coumarin derivatives are generally contraindicated because of their ability to pass the placental barrier.

There are other contraindications that are somewhat less stringent. Here the urgency of therapy must be balanced against the risk of hemorrhage that is involved. These include moderate hypertension, diabetes, vasculitis, subacute bacterial endocarditis, renal and liver disease, surgery in general, but particularly of the biliary tract in the presence of hepatic failure, and surgery of the lung and prostate. Pericarditis complicating acute myocardial infarction deserves special consideration in view of the possibility of hemopericardium consequent to the use of the coumarin drugs. Extensive bleeding into the thyroid gland has also been observed in thyrotoxic patients who have received therapeutic I^{131} while on anticoagulant therapy.

In addition there is a group of disorders in which adequate preparation before anticoagulants are given may reduce the hazards of therapy. These include: congestive heart failure, malnutrition, vitamin C and K deficiencies, ulcerative colitis, sprue, steatorrhea, and pancreatitis.

It is important to realize that this guide should not be taken too literally. The question as to whether in a given patient the need for anticoagulant therapy outweighs its hazards requires sound clinical judgment.

Questions and Answers

1. *Question: Among Laboratory Tests* Currently Available, Which is the Most Satisfactory and Practical as a Guide to the Dosage of Coumarin-type Drugs?*

Answer: Since the anticoagulant action of these agents is predicated upon their decreasing the concentration of factors II, VII, IX, and X (tables 1 and 2), the ideal test would be one that measures all of these activities in a simple, inexpensive procedure that is least susceptible to technical error. Until recently, the Quick whole-plasma prothrombin time, which measures all of these factors except IX, has been considered as best fitting these requirements, and most of our information regarding coumarin therapy has been obtained with this test. The "Thrombotest," recently devised by Owren, includes the measurement of factor IX, thus theoretically providing a more comprehensive assay of the pharmacologic effects of these drugs. It has the further advantage that it can be performed on capillary blood at the bed side. At present there is insufficient experience to state definitively whether the "thrombotest" is superior to the Quick prothrombin determination as a guide either to the antithrombotic action or the hemorrhagic complications of coumarin-type drugs.

2. *Q. Why Are There So Many Different Technics for Performing the Quick Prothrombin Time? What Method Is Considered Most Desirable?*

*Although available in certain centers abroad, these concentrates are not yet obtainable in the U.S.A. It is likely that further development will make them soon available and extremely useful for this and other purposes.

†This latter interdiction does not apply to pulmonary embolism, or to the hemoptysis secondary to mitral stenosis, but refers rather to hemorrhage due to primary parenchymatous disease of the lungs.

*Details of the several tests referred to in this pamphlet are found in *Coagulation of Blood. Methods of Study* in the Bibliography.

A. Numerous variations are related to different thromboplastic extracts employed, technical differences in the actual mixing of reagents, the end point selected for a definitive result, and the interpretation of the observed clotting time in terms of the per cent prothrombic activity. For gauging the effect of the "prothrombinopenic" drugs, the determination on *whole* plasma by the original Quick procedure is generally considered best. One major point to be considered in the procedure is the potency of thromboplastic extract used. The material should give a prothrombin time on normal plasma of between 10 and 14 seconds. Less potent extracts are apt to give erratic results. The value on normal plasma in seconds should always be expressed side by side with that for the test plasma.

3. *Q. Should the Results of the Prothrombin Determination Be Reported in Seconds, or Per Cent of Prothrombic Activity?*

A. Either method is satisfactory. The advantage of reporting in seconds is that it provides an indication of the potency of the thromboplastin, and at the same time indicates whether the desired elevation in prothrombin time has been achieved. It should be elevated one and a half to two times the value of the control plasma. Another advantage in reporting the prothrombin values in seconds is that the results obtained in one laboratory can be compared with those obtained on the same patient in another laboratory, provided the control value of the other laboratory is known and the thromboplastin employed in the test is derived from the same species.

Reporting in per cent, on the other hand, permits a simple assessment of the day-to-day and week-to-week trend of the effect of the drug. For these reasons it is best to request both time and per cent values, even though this increases the amount of data to be recorded.

4. *Q. What Are the Important Technical Factors in Obtaining and Processing Blood Samples for Prothrombin Time Determinations?*

A. The observed prothrombin time in the Quick procedure reflects the concentrations of factors II, V, VII, X, as well as factor I (fibrinogen). Except for fibrinogen, all may be influenced by lapses in technic. If the vein is not entered directly in performing the venipuncture, if delay is encountered between drawing the blood into the syringe and thorough mixing with the anticoagulant, if tissue juice is drawn back even in minute amounts into the needle as a result of not entering the vein directly, or, if the needle slips out of the vein during blood withdrawal, factor VII may be activated, thus giving a falsely low (accelerated) prothrombin time. Conversely, prothrombin or factor V may be partly consumed as a result of such technical failure, giving a falsely elevated (retarded) prothrombin time. Under any of these circumstances, therefore, it is advisable to make a completely new attempt with *another* syringe and needle. A delay of more than 2 to 4 hours between the drawing of the blood and its analysis in the laboratory can result in a false determination on whole plasma because factor V is labile, especially at room temperature, and may deteriorate, thus yielding falsely elevated prothrombin times. This technical difficulty can be circumvented, however, by a modification of the Quick test in which ample amounts of factor V are added in the assay.

Q. How Often Should Prothrombin Times Be Performed?

A. This question has special significance with regard to "long-term" therapy. After the daily prothrombin determinations establish the individual dose requirements (usually in about a week), the tests can be spaced to every other day, subsequently to twice weekly and eventually once every 2 weeks. On "long-term" therapy, less frequent determinations are permissible but only after the physician has become sufficiently familiar with the patient's needs, his stability, and after he is assured of the patient's capacity and willingness to cooperate. If the results indicate stability, determinations can be safely performed every 2 weeks. There is some difference of opinion as to the advisability of longer intervals. Intervals longer than 3 weeks incur substantial risk of lack of adequate control. Determinations spaced at more than 4 weeks should be reserved for extremely few individuals under special circumstances.

For those patients contemplating an extended vacation, or whose occupation or other circumstances demand considerable travel, the doctor should refer the patient to a reliable physician elsewhere, or familiarize himself with laboratories in other cities where accurate determinations can be obtained for his patient.

6. *Q. Why Do Prothrombin Times Fluctuate So Widely?*

A. The many variables that influence the prothrombin time can be briefly listed as follows: the biochemical and physiologic properties of "prothrombinopenic" drugs, including their solubility, absorbability, transport and fixation in the liver; their speed of metabolism, degradation, and excretion; the nutrition of the patient with regard to vitamin K_1; the synthesis, original stores, and in vivo turnover rates of the various clotting factors affected; and pathologic processes in the recipient. Any of these may considerably and acutely vary in a given individual from time to time. Also to be considered are lapses in technic.

7. *Q. What Is the Significance of the Term "Whole" as Contrasted with "Dilute" Prothrombin Time?*

A. The term "whole" is applied to determination of the prothrombin time on *whole* plasma obtained from centrifuged oxalated or citrated blood. The observed value reflects the concentrations of factors I, V, II, VII, and X. Of these, the last three are influenced by the coumarin-type drugs. To eliminate test variations dependent on fibrinogen or factor V, several procedures have been devised in which these two factors are provided in optimal amounts to the test system by diluting the test plasma with adsorbed normal plasma (fig. 1). In this way a more reliable assay for the three coumarin-affected factors is provided. Moreover, such dilution permits more precise quantitation by setting the conditions of the test at a range where the prothrombin time can be more sharply correlated with the concentration of these clotting factors. The dilution of the test plasma with adsorbed normal plasma, rather than with physiologic saline, thus minimizes this possible error while providing a better endpoint.

8. *Q. There Is Considerable Reference in the Literature to "One-Stage" and "Two-Stage" Methods of Measuring Prothrombin. What Does This Terminology Signify, and Has It Any Relevance to Anticoagulant Therapy?*

A. The term "one-stage" refers to the commonly employed Quick procedure or modifications thereof, for measurement of prothrombic activity in one step: by the addition of thromboplastin and calcium to plasma, and measurement of the velocity of clotting (prothrombin time). The term "two-stage" applies to a procedure, originally devised by Seegers and colleagues, in which the prothrombin determination is made in two stages: in the first step, a suitably diluted sample of plasma is mixed with thromboplastin and calcium, which converts *all* the prothrombin to thrombin. In the second step, the amount of thrombin formed is then measured by its clotting of a standardized fibrinogen solution. This method, of great value in coagulation research, is specific fqr measuring prothrombin, but does not include the other factors influenced by the "prothrombinopenic" drugs. Since these other factors are thought to play an important role in anticoagulant action, the Quick one-stage procedure, by measuring more of the factors, is considered preferable as a practical guide to coumarin therapy.

9. *Q. What Is the "P-P" Test of Owren? Is It Preferable to the Quick Test?*

A. This is essentially a modification of the Quick one-stage procedure. Originally devised by Owren, it was intended to measure both prothrombin (factor II) and proconvertin (factor VII). We now know that it also includes factor X (Stuart). It is therefore as satisfactory as the Quick test for measuring these factors. The Quick procedure, however, gives additional information regarding factors I and V.

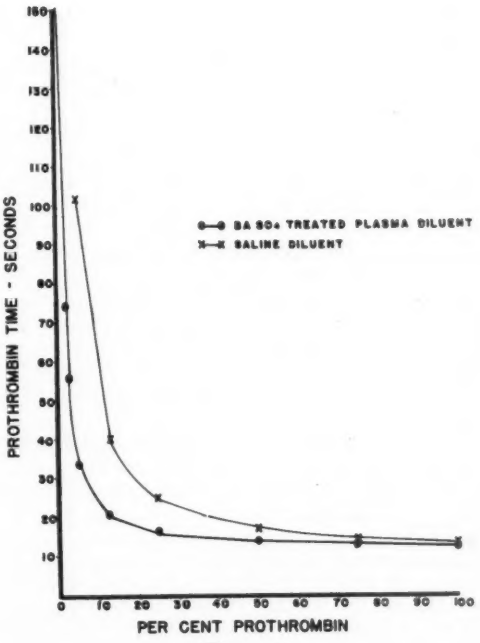

Figure 1

Correlation between prothrombin time and prothrombic activity. Human brain thromboplastin used. Saline curve (x—x) pertains to pooled normal human oxalated plasma diluted with physiologic saline in amounts selected to give the indicated per cent. The other curve (●—●) indicates similar dilutions with adsorbed plasma devoid of factors II, VII, IX, and X. Unadsorbed, and thus remaining in the modified plasma in normal concentration, are factors I and V. This probably accounts for the difference in configuration of the curves. Note the rapidly rising prothrombin time as the prothrombic activity declines below 20 per cent of normal.

10. *Q. What Is Meant by the Term "Therapeutic" Range of Prothrombin Activity?*

A. Clinical experience indicates that an activity of 10 to 20 per cent of normal is compatible with normal hemostasis, assuming *all other hemostatic functions to be normal:* platelet count, vascular function, etc. To be reasonably certain that the activity does not fall below the lower level, in view of the commonly experienced variations in activity (discussed in the text) the physician should strive

for an activity of 15 to 25 per cent of normal (approximately one and one-half to two times the control value in seconds). That this represents retarded coagulation is evident from the curve correlating prothrombic activity with the prothrombin time (fig. 1). At or below 20 per cent activity, the velocity of thrombin elaboration from prothrombin becomes progressively and rather sharply retarded. Although values below 10 per cent prothrombic activity give even slower speeds of clotting, such levels increase the risk of bleeding progressively as the prothrombin time rises. In reality the "therapeutic" range is defined in a negative sense; namely, the maximal reduction in prothrombic activity compatible with satisfactory hemostasis.

11. *Q. What Is the Desired "Therapeutic" Level with Heparin?*

A. Here again we are guided by experience. As with the coumarin drugs, the objective is maximal interference with coagulation with minimal risk of hemorrhage. When the clotting time is two times the normal value obtained in a given institution with its own particular technic and equipment, clotting is markedly retarded, yet there is no serious danger of bleeding. Temporary spikes above this level can also be tolerated without undue risk of hemorrhage. As with the prothrombin time, meticulous technic must be followed to avoid false clotting times: glassware, syringe, and needle must be clean, the vein must be entered by "primary intention," the blood must flow freely into the syringe with minimal frothing, the blood-filled clotting-time tubes must not be agitated, and the test must be completed promptly at the bedside.

There is no getting away from such stringent technical requirements, with either heparin or the coumarin drugs.

12. *Q. Can the* Whole Blood Clotting Time *Be Used Instead of the Prothrombin Time As a Guide to* Coumarin *Therapy?*

A. No. For heparin, the clotting time is invaluable as a guide. It is also useful in screening patients for a hemorrhagic diathesis, because an elevated clotting time indicates a profound coagulation disturbance. It should be emphasized, however, that many a serious defect can be masked by a normal clotting time. This is particularly true of "hypoprothrombinemic" states. Here the glass clotting time is most often normal despite marked depression of the coumarin-vulnerable clotting factors to a degree sufficient to cause bleeding. Under these circumstances the prothrombin time can be markedly elevated despite a normal glass clotting time. Although the clotting time in silicone-coated tubes will be distinctly prolonged by coumarin therapy, the test under these conditions requires a long interval of observation by the technician and meticulous attention to technical details. For these reasons the prothrombin time determination is preferred as the guide to the use of coumarin drugs.

13. *Q. As a Guide to Heparin, Is the Determination of the Clotting Time by the Capillary Tube Method As Satisfactory As Venous Blood in Regular Size Clotting-Time Tubes?*

A. There is general agreement that the capillary tube method is unreliable, and therefore should not be used.

14. *Q. Are There Any Tests Besides the Prothrombin Time Which Should be Periodically Performed on a Patient Who is on Long-Term Coumarin Therapy?*

A. Although the prothrombin determination is the cardinal laboratory guide to coumarin therapy, it is known that bleeding may occur in some individuals despite maintenance of the prothrombic activity at levels considered compatible with normal hemostasis. The reason for this is obscure; it is probably attributable to factors outside of blood clotting that play important roles in the over-all hemostatic mechanism, or to the fact that some other clotting factor is affected which is not measured by the prothrombin assay. Accordingly, other tests are valuable. The hemoglobin level, as well as examination of the urinary sediment and stool for occult blood, should be determined periodically.

15. *Q. Do the Anticoagulants Affect Important Laboratory Tests Such as Measurements of the Formed Elements of the Blood, Sedimentation Rate, Electrocardiogram, or Agglutination Tests?*

A. As far as is known neither heparin nor coumarin derivatives significantly alter the parameters referred to. Heparin does, however, bind complement, and thus may interfere with certain serologic tests. Also, heparin is said to increase the resistance of red cells to hypotonic salt solutions.

16. *Q. What Procedure Should Be Followed in a Patient on Long-Term Coumarin Therapy Who Needs Minor Surgery Such as Extraction of a Tooth or Removal of a Wen?*

A. If the procedure is elective and can be delayed for several days, the anticoagulant should be discontinued, the prothrombin time determined daily, and the procedure performed when the prothrombic activity rises above 30 per cent. It is generally agreed that inordinate bleeding will not occur at or above this level. Therapy can be resumed on the day of surgery and followed daily until "therapeutic" levels are again obtained. If the procedure cannot be delayed, the administration of a small dose of vitamin K_1 (5 mg.) will hasten the return of prothrombic activity. In any event, the procedure should be done *only after* the pro-

thrombin determination indicates that it is safe to proceed. It should be mentioned, however, that some investigators believe that these minor procedures can be performed safely at the "therapeutic" range of prothrombic activity.

17. *Q. Does the Same Hold True for Major Surgery?*

A. The same considerations hold here also. If the procedure is elective, the patient can be properly prepared by postponing the operation for several days until the prothrombic activity rises above 30 per cent. If, on the other hand, the procedure is of an emergency nature, prompt correction of the drug-induced defect can be achieved by transfusion with blood or plasma, supplemented by intravenous vitamin K_1 (25 to 50 mg.). Since the clotting factors involved are relatively stable, it is not necessary that the blood be fresh; ordinary bank blood or plasma is adequate. The amount administered should be sufficient to assure a prothrombic activity of at least 30 per cent. In an average adult, 3 or 4 units of blood or plasma are likely to be necessary.* Moreover, since it is possible that substantial blood loss may occur during the operative procedure, thus depriving the patient of prothrombin and the other clotting factors, additional quantities of blood or plasma should be readily available, and used during and following surgery, as indicated by clinical and laboratory observations.

Also of considerable value is the local use by the surgeon of topical thrombin applied liberally to oozing surfaces should undue bleeding be encountered.

As to resumption of anticoagulant therapy, the same procedure can be followed with major, as with minor, surgery with certain exceptions. Special caution is indicated in surgery involving lung, prostate, biliary tract, and extensive raw surfaces.

An alternative approach is feasible: the physician may choose to shift from coumarin to heparin therapy.

18. *Q. How Long Must One Wait after Eye or Brain Surgery before Anticoagulant Therapy Can Be Resumed?*

A. Although the general principles outlined in questions 16 and 17 regarding the reinstitution of therapy after surgery in general will also apply here, it is advisable to wait longer in eye or brain surgery because minor bleeding, which would be of little significance in other parts of the body, may have dire consequences in these organs.

19. *Q. How Would You Handle a Heparinized Patient Who Needs Prompt Surgery?*

A. Since the anticoagulant action of heparin is relatively transient, a lapse of 3 or 4 hours following the last dose (assuming it was administered intravenously) is sufficient protection against hemorrhage. This should be confirmed by a clotting time determination prior to operation. If surgery cannot be deferred for several hours, protamine sulfate should be administered (see p. 127). Other agents, such as toluidine blue or neutral red, are also effective, *but blood and plasma have no antiheparin effect.*

Clinical experience indicates that heparin can be resumed safely 24 hours or, on occasion, even immediately after surgery. Under special circumstances such as in vascular or cardiac surgery, heparinization may be advisable throughout the procedure. Conversely, any anticoagulant therapy following ocular or central nervous system surgery is distinctly hazardous and generally contraindicated.

20. *Q. Do the Anticoagulants Affect Menstruation?*

A. Frequently menstrual flow is increased and prolonged. This is of little clinical significance unless there is disease of the reproductive tract such as fibroids or cervical ulceration. However, drug-induced, excessive menstrual flow may eventually cause anemia from chronic blood loss, especially in long-term therapy. This can be treated by supplements of iron or by blood transfusions.

21. *Q. How Do You Handle a Hemorrhagic Complication in a Patient on Long-Term Anticoagulant Therapy, in Whom You Would Like to Resume Therapy after the Bleeding Is Controlled?*

A. The patient should be informed prior to treatment of the possibility of bleeding from the nose, gums, mouth, and vagina as well as into the urine, stool, and skin. The patient should always carry with him vitamin K_1 tablets (Mephyton) of 5 mg. each. The individual should promptly notify the doctor of any bleeding. The physician can then decide on the appropriate course of action: discontinuance of the drug, the immediate use of the antidote and in what amounts, or the use of hospital facilities for the appropriate laboratory studies or the administration of blood, plasma, or intravenous antidotes. When bleeding has stopped, anticoagulant therapy can be resumed, guided again by the usual laboratory determinations.

The physician must always be alert, furthermore, to the possibility of bleeding arising from other pathology.

22. *Q. Are There Any Special Recommendations Concerning Records to Be Kept by the Patient or By the Physician?*

A. The patient should not only be informed

*In patients with limited cardiac reserve such volumes may be dangerous.

as to the general effects, nature, name, dose, and strength of the medication he is receiving, but should carry a card stating that he is on therapy, the drug and dose that he is taking, and that it may predispose him to undue bleeding in the event of accident. For the physician, a simple record form designed specifically for recording anticoagulant data will be found useful.

23. *Q. Is There Any Food with Anticoagulant Properties?*

A. For cattle, yes (spoiled sweet clover); for man, no.

24. *Q. Besides Those Foods That Are Rich in Vitamin K_1, are There Any That Make the Blood Hypercoagulable? What is the Role of Fats in Clotting?*

A. The vitamin K_1-rich foods have already been referred to (p. 128). There is only suggestive evidence that other foods have clot-prompting properties. The role of dietary lipids in coagulation is still obscure. Many observers report that after a fatty meal, in hyperlipemic states or following the addition of lipid material to blood in vitro, clotting is in some respects accelerated. The relevance of these observations to intravascular coagulation, however, is unresolved, and therefore, at present, the dietary management of patients should be predicated on other factors besides the possible effect on clotting.

25. *Q. Is It True That Salicylates Have a "Prothrombinopenic" Effect? If So, Does This Preclude the Use of All Salicylates in Patients Receiving Coumarin-Type Drugs?*

A. Salicylates in large doses are mildly "prothrombinopenic." On the other hand, "hypoprothrombinemia" of clinically significant degree is not observed even in those patients taking large amounts of salicylates for rheumatic fever or arthritis. Nevertheless, in view of the tendency toward gastric bleeding occasionally encountered in patients on salicylates, presumably attributable to local gastric irritation, it would seem wise to limit or omit salicylates in patients on anticoagulant therapy.

26. *Q. Besides Salicylates, Are There Any Other Commonly Used Drugs That Influence Coumarin Therapy?*

A. The question of antibiotics, already alluded to (p. 129) is significant in that they can enhance the action of coumarin derivatives by decreasing the supply of vitamin K_1 available from intestinal bacterial biosynthesis. With regard to steroids there is considerable experimental evidence that they increase the sensitivity of animals to the "prothrombinopenic" effects of these drugs, as well as the incidence of hemorrhagic complications. These observations do not, however, necessarily preclude coumarin therapy, but rather focus attention again on the importance of individualization of therapy.

27. *Q. Are There Any Drugs That Accelerate Intravascular Coagulation?*

A. The acceleration of clotting by stress and epinephrine has been known since the early work of Cannon and others. It has also been observed that in isolated clotting systems some commonly used drugs, such as digitalis, mercurial diuretics, and benadryl may accelerate clotting kinetics. As yet there is no clear-cut evidence that these effects are clinically significant. Recently, chlorpromazine and reserpine have been implicated in causing thrombosis, although the actual underlying mechanisms are unknown. As the question implies, the physician should remain alert to the possibility that these and other commonly used therapeutic agents may actually precipitate or aggravate intravascular coagulation.

28. *Q. How Should Heparin Be Administered?*

A. Heparin may be administered intravenously by constant infusion, by intermittent injections on schedules ranging from every 2 to 8 hours, and by the intramuscular and subcutaneous routes in a variety of menstruums. Based on control of the antithrombotic effect, reliability, safety, and unpleasant side reactions, the intravenous route on 4 or 2 hourly schedule is at least as satisfactory, if not superior, to any other regimen.

Intermittent intravenous administration may be facilitated by the use of an indwelling plastic catheter inserted into a superficial forearm vein. Daily examination of these catheters will minimize the risk of sepsis involved in their use. The initial dose requirement is usually 50 to 75 mg.; subsequent individual doses to be injected (25 to 125 mg.) are determined by the clotting time. The dose selected should be so calculated as to induce, 4 hours after its injection, a clotting time of approximately twice that of the pretreatment value. After this dose requirement has been established, the clotting time should be determined once daily 4 hours after the last dose to exclude a possible increase in the anticoagulant effect of the drug and to allow for variations in heparin requirements during the course of treatment. In contrast to the coumarins, laboratory tests guiding heparin therapy do not require special reagents or a highly trained technician.

29. *Q. Many Believe That Heparin Is Just As Effective When Administered Subcutaneously As When Given Intravenously. Would It Not Be Distinctly Advantageous to Use the Subcutaneous Route Rather Than the Intravenous If the Former Is Satisfactory? Why Is There This Difference of Opinion?*

A. In contrast to intravenous administration, the subcutaneous route occasionally results in a

more erratic clotting time elevation. Also, local pain, ecchymoses, and rarely neuritis may occur at the injection site. This may be compounded if other medications are also being administered by this route. Moreover, reversing the anticoagulant effect with protamine, should this be necessary, is more difficult after subcutaneous than after intravenous administration (see p. 127). Finally shifting from heparin to coumarin-type agents is less difficult when the route of heparin administration is intravenous. For these reasons the intravenous route is considered preferable, although it is recognized that satisfactory elevations of the clotting time may be obtained by the subcutaneous or intramuscular administration of heparin. New heparin preparations for subcutaneous use are currently under investigation.

At present heparin can effectively be administered intravenously for several weeks.

30. *Q. Are There Situations Where Heparin Is Preferable to Coumarin-Type Compounds? How Should a Patient Be Changed from Heparin to a Coumarin?*

A. Heparin is the drug of choice for emergency situations in which immediate therapy is indicated. Other circumstances where this agent has advantages over the coumarins are discussed in the text. In addition, heparin is generally more advantageous when laboratory facilities are limited.

When the physician contemplates shifting to coumarin drugs after initiating treatment with heparin, both agents are given initially until the full anticoagulant effect of the coumarin becomes manifest. Some observers believe that heparin can then be discontinued (i.e., 1 or 2 days after the beginning of coumarin therapy), whereas others believe that heparin should be continued for another 4 to 6 days after the anticoagulant effect of the coumarin drug has become apparent. In either event, the dose of each agent should be regulated by the appropriate laboratory guide. It should be recognized that the coumarin agent, although it does not interfere with the clotting time determination, may make the patient more sensitive to heparin. Furthermore, the ability of heparin to affect the prothrombin time determination requires that the clotting time is not affected by heparin (4 or more hours after its administration). This specific problem is difficult to overcome if the patient is receiving heparin by either subcutaneous or intramuscular routes because the sustained elevation of the clotting time indicates continued heparin effect which interferes with the accuracy of the prothrombin determination.

31. *Q. What Is the So-Called "Rebound Phenomenon"?*

A. There is an impression, held by many observers, that following the abrupt discontinuance of anticoagulant therapy, there is a significant incidence of recurrent thrombosis. It has also been observed that certain clotting factors may attain abnormally high levels after cessation of coumarin therapy. It has also been observed that discontinuing heparin may result in an abnormally shortened clotting time. These elevations following cessation of coumarin therapy are said to be even more pronounced if the termination of therapy is hastened by the administration of vitamin K_1. This has been interpreted as a "rebound" effect. Whether this phenomenon is the cause of the observed recurrent thrombosis is unknown. Nevertheless, these impressions and observations provide sufficient basis for the recommendation that both heparin and coumarin be discontinued gradually rather than abruptly, and that the use of vitamin K_1 in stopping therapy be avoided where possible.

32. *Q. Are There Any Laboratory Tests for "Hypercoagulability"?*

A. A variety of in vitro coagulation abnormalities has been observed in patients with thrombotic tendencies. These include the increased resistance of the patient's blood to the clot-retarding effects of heparin added to blood in vitro (the heparin-tolerance test); elevated levels of factors I, VII, and X; accelerated generation of intrinsic thromboplastin; faster than normal prothrombin time; shortened glass and silicone clotting times; and increased platelet stickiness. These abnormalities, however, do not correlate sufficiently with intravascular coagulation to permit their acceptance as in vitro assays of thrombosis. Accordingly, there is at present no reliable test to indicate the impending, incipient, or actual thrombotic state.

33. *Q. Is There an Age Limit to the Use of Anticoagulants?*

A. Here again one can be too arbitrary. There is little question that in advancing years obstacles arise that make therapy more difficult, if not hazardous. Older patients are apt to be forgetful and uncooperative, they may have a faulty hemostatic mechanism by virtue of loss of skin elasticity and greater fragility of blood vessels (purpura senilis). Renal function is apt to be compromised, and dietary irregularities are fairly common in older individuals. On the other hand, the usually accepted indications for employing anticoagulants become more common. Age per se should not impose limitations on the use of anticoagulant drugs.

Summary

The physician who undertakes anticoagulant therapy tampers with one of the most important homeostatic functions of the body. In so doing, he subjects the patient to the

calculated hazard of possible hemorrhage balanced against the risks of the thrombosis or embolism that he seeks to prevent or treat. Agents currently employed are heparin and coumarin-type compounds. These two categories of anticoagulants act at different sites of the coagulation mechanism, are administered differently, are metabolized differently, are reversed by different antidotes, and their effects are measured by different tests.

Certain facts about which the physician should be adequately informed have been presented regarding the hemostatic mechanism; the physiology and pharmacology of the anticoagulants, especially as they may explain the wide variation in individual response; certain aspects of methodology; and the various practical problems involved in therapeutic management. Emphasis has been placed on the importance of individualization of treatment, careful clinical observation, and frequent reliable laboratory tests as guides to proper therapy.

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Varying results depend on the greater or less diminution of the volume of air usually contained in the thorax (lungs); and the cause which occasions this diminution, whether solid or liquid, produces analogous results to those obtained by striking a cask, for example, in different degrees of emptiness or fulness: the diminution of sound being proportioned to the diminution of the volume of air contained in it.—From *On Percussion of the Chest.* Published in 1761. Translated by John Forbes, M.D. *In: Classics of Medicine and Surgery.* New York, Dover Publications, Inc., 1959, p. 128.

ABSTRACTS

CONGENITAL ANOMALIES

Spear, G. S.: Glomerular Alterations in Cyanotic Congenital Heart Disease. Bull. Johns Hopkins Hosp. **106**: 347 (June), 1960.

Histologic studies were made of the kidneys obtained at necropsy from 17 patients with cyanotic congenital heart disease and one patient with primary pulmonary hypertension. The lesions were similar and consisted of hypercellularity and intercapillary deposition of eosinophilic material, particularly in the axial stalk of the mesangium; many glomeruli were congested and enlarged, the basement membranes were altered and a few hilar arterioles were dilated. The histologic pattern was rather characteristic, and was not found in patients with cyanotic heart disease or in other primary cardiac or renal disease processes. No correlation was apparent between the severity of the disease process and the degree of arterial oxygen desaturation. The pathogenesis of the glomerular lesions remains obscure, since there were no associated autopsy, clinical, or laboratory findings that were helpful in determining the etiology of these changes.

KARPMAN

CONGESTIVE HEART FAILURE

Effersoe, P., Ristensen, H. S., and Lassen, H. C. A.: Effect of Oxygen Therapy on Oedema in Patients with Cor Pulmonale: Brit. M. J. 1: 1469 (May 14), 1960.

Three case histories are presented in an effort to demonstrate the effectiveness of oxygen therapy combined with artificial ventilation in reducing edema of patients with cor pulmonale who are resistant to usual measures. The first patient was a 40-year-old man admitted with diffuse pulmonary fibrosis, advanced pulmonary insufficiency, and cor pulmonale. Prior to admission he had been treated with aminophylline, digitalis, oxygen, and mercaptomerin for his dyspnea and edema which gradually became worse in spite of these medications. He was treated with oxygen and a tank respirator on three occasions and each time his edema promptly subsided. While hospitalized, he received digitalis but no diuretic therapy. The second patient was a 38-year-old woman admitted with increasing dyspnea, pulmonary insufficiency, and jugular stasis but without edema, bronchitis, or pneumonia. She was placed on intense oxygen therapy beginning with 2 liters per minute and increasing to 4 liters per minute for 16½ to 18 hours per day. This resulted in reduction of the edema even though the pCO_2 increased and the pH fell during this treatment. The third patient was a 52-year-old woman with severe pulmonary insufficiency but no active pulmonary disease. She had moderate edema and was treated with low-salt diet and bed rest. Oxygen treatment was begun 6 days later because her condition remained stationary. Urine volume increased somewhat during the oxygen therapy and electrolyte excretion was markedly increased 5 to 6 days after treatment started. The edema subsided entirely at this time.

Oxygen therapy for the elimination of cardiac

edema has been previously described. The basic mechanism appears to be that tissue hypoxia conditions the formation of cardiac edema. In this respect supplying oxygen acts to remove the hypoxia and therapy relieves the edema.

KRAUSE

Fragge, R. G., Kopel, F. B., and Iglauer, A.: Serum Glutamic Oxalacetic Transaminase (SGO-T) in Congestive Heart Failure: Clinical Study and Review of the Literature. Ann. Int. Med. **52**: 1042 (May), 1960.

Forty-three patients with congestive heart failure and without evidence of disease that may elevate the serum glutamic ovalacetic transaminase (SGO-T) activity were evaluated to determine the significance of elevated SGO-T titers in this condition. Elevated levels were present in 13 patients. The levels were particularly elevated during acute exacerbations of chronic congestive heart failure. The levels were elevated in patients with right, left, and combined heart failure although the highest levels were found in chronic lung disease with right heart failure. Changes in the liver compatible with acute passive congestion were found in a patient with right heart failure; it was thought that these histologic changes accounted for the high SGO-T activity.

KALMANSOHN

Makela, T. E., Hakkila, R. L., and Hakkila, J.: Absorption of I^{131} - oleic Acid in Congestive Heart Failure. Acta med. Scandinav. **167**: 121, 1960.

The rate of absorption into the blood of I^{131} triolein was markedly lower in persons with congestive heart failure than in control subjects. The absorption of this substance was impaired in other conditions such as pancreatic insufficiency and was influenced by bile secretion. On the other hand, oleic acid did not require pancreatic secretion and was readily absorbed from normal intestinal mucosa. Therefore, I^{131}—labeled oleic acid was administered to 10 control subjects and 17 patients with congestive heart failure. There was no difference in the absorption between the control subjects and the patients with heart failure. In two subjects both iodinated substances were administered, and the absorption of oleic acid was found to be markedly better than that of the triolein. It was suggested that this impairment of absorption of triolein in the presence of congestive heart failure was due chiefly to "digestive factors."

SHEPS

CORONARY ARTERY DISEASE

Altman, G. E., Riseman, J. E. F., and Koretsky, S.: Sublingual Erythrol Tetranitrate in the Treatment of Angina Pectoris. Effect of Varying the Dose and Rate of Administration. Am. J. M. Sc. **240**: 66 (July), 1960.

The effect of sublingual erythrol tetranitrate on angina pectoris was evaluated, with tablets that took a long time to dissolve, with tablets that dissolved rapidly, and with a powder. Sublingual absorption was more rapid than buccal absorption. The powder was of no advantage over the rapid absorption tablets. Following the administration of a single 15-mg. dose, the capacity for increased exercise tolerance began after a few minutes, was at a peak at 1 to 2 hours, and decreased over 3 to 4 hours. There was no difference with the tablets with delayed absorption. The maximally effective dose varied between 5 to 15 mg. in different patients. Doses greater than this were of no increased therapeutic value but increased the incidence of side effects. In a few subjects the following side effects were noted: local burning, headache, dizziness, faintness, and hypotension. Following the administration of doses greater than 5 mg., there was often a moderate decrease in systolic blood pressure which lasted a variable length of time, depending on the dose.

SHEPS

Bouvrain, Y., Fortin, P., Perrotin, M., and Richard, A.: Pleuro-pericarditis following Myocardial Infraction. Arch. mal. coeur **53**: 134 (Feb.), 1960.

Of 289 persons with myocardial infarction, three developed pleuro-pericarditis 9 to 30 days after onset of the acute infarction. This was accompanied by fever, accelerated sedimentation rate, pericardial friction rub, increased heart size, pleural effusion and, in one patient, by joint pains, eosinophilia, and prolongation of the P-R interval. In one patient low voltage of the QRS complex appeared. Administration of adrenocortical steroids caused rapid regression of all symptoms. These findings were considered to represent an allergic reaction to proteins liberated from the infarcted cardiac muscle. It is possible that instances of fever without apparent cause, following myocardial infarction, belong in the same category.

LEPESCHKIN

Cohen, L.: Serum Phospholipids in Coronary Artery Disease. J. Lab. & Clin. Med. **54**: 352 (Sept.), 1959.

Phospholipids are classified into two groups:

those containing choline (CCPL) and those containing serine, ethanolamine, or inositol (NCCPL). The physiological role of phospholipids is uncertain. Although they are an integral part of lipoproteins and therefore a necessary cofactor in the lipolytic activity of lipoprotein lipase, a more interesting role is their yet-to-be-defined role in normal coagulation and intravascular clotting, as suggested by previous in vitro and in vivo experiments. The total phospholipids, as well as cholesterol totals, were determined in 20 patients and 36 controls. Choline was measured by microbiological assay, and lipid phosphorus was determined colorimetrically. The patient group consisted of 18 men and two postmenopausal women, 32 to 59 years of age, with coronary artery disease manifested by angina pectoris or previous myocardial infarction. The control group consisted of 36 male physicians and laboratory workers, 20 to 56 years of age, subdivided into a group 20 to 29 years, and another of 32 to 56 years of age. Although neither CCPL nor NCCPL alone revealed significant deviation from the control groups, combined CCPL and NCCPL determinations showed a statistically significant rise in patients with coronary artery disease. The mean serum phospholipids in these patients was greater by 10.1 per cent than in the two control groups. This figure is in agreement with previous reports. Serum cholesterol values were also elevated in the group with coronary artery disease. The results could not discriminate which of the phospholipids accounted for the rise in each fraction. The author suggests that the increase in CCPL may be explained by an increased sphingomyelin content.

MAXWELL

Davison, K., and Smith, B. J.: Myocardial Infarction after Acute Gastrointestinal Haemorrhage. Brit. M. J. 1: 1400 (May 7), 1960.

The clinical features and autopsy findings are presented of three cases of myocardial infarction that occurred after acute gastrointestinal hemorrhage. The pathogenesis of cardiac disturbances with gastrointestinal bleeding is probably related to inadequate coronary blood flow secondary to a reduction in circulating blood volume. When this reduction of blood volume is unduly prolonged or very great, myocardial necrosis is likely to follow. At first there is a relative inadequacy of coronary blood flow ("acute coronary insufficiency") which when it becomes protracted leads to myocardial infarction. Experimentally, a 35 per cent reduction in coronary blood flow is the critical level for the production of electrocardiographic changes. Treatment consists of early and adequate intravenous blood replacement to prevent myocardial infarction or even after myocardial infarction has occurred, since early restoration of coronary blood flow will restrict the area of myocardial necrosis.

KRAUSE

de Micheli, A., Piccolo, E., Cocco, F., Bisteni, A., and Sodi Pallares, D.: Disturbances of Rhythm and of Conduction in Myocardial Infarction. Arch. Inst. cardiol. México 30: 151 (Mar.-Apr.), 1960.

The frequency of the disorders of cardiac rhythm and conduction was studied in 400 patients with myocardial infarction. The closest relationship was found between myocardial infarction of the diaphragmatic wall and atrioventricular block and between septal infarction and bundle-branch block. The mortality increased when myocardial infarction was complicated by these disorders, particularly by complete atrioventricular block or by paroxysmal ventricular tachycardia.

BRACHFELD

Fife, R., Howitt, G., and Stevenson, J.: Iproniazid in Treatment of Angina of Effort. Brit. M. J. 1: 692 (Mar.), 1960.

Iproniazid was used to treat 51 well-documented cases of angina pectoris. Previous reports on the use of this drug offer conflicting results. This study, with placebo controls, proved no great efficacy for iproniazid except possibly in severe cases. Side effects were frequent and troublesome and actually to some extent nullified the double-blind design of the therapeutic trial.

KRAUSE

Friedman, M. St. George, S., Byers, S. O., and Rosenman, R. H.: Excretion of Catecholamines, 17-Ketosteroids, 17-Hydroxycorticoids, and 5-Hydroxyindole in Men Exhibiting a Particular Behavior Pattern (A) Associated with High Incidence of Clinical Coronary Artery Disease. J. Clin. Invest. 39: 758 (May), 1960.

The urinary excretion of 17-ketosteroids, 17-hydroxycorticoids, 5-hydroxyindole, epinephrine, and norepinephrine were measured in a group of 12 men exhibiting an overt behavior pattern (pattern A, characterized by excessive and competitive drive and an enhanced sense of time urgency) and a group of 12 men exhibiting a converse type of behavior pattern (pattern B). The catechol excretion of both groups of men were essentially identical when the specific milieu was not provoking (i.e., bed rest) but a far greater increase of norepinephrine occurred in the urine of the men exhibiting pattern A if the specimens were collected during the times of

stress and tension (i.e., during the working hours). These findings suggested that the excess catechol excretion in the pattern A group was a phasic rather than a fixed phenomenon and that 24-hour urine collections might not have revealed these phasic differences. The authors suggest that the phasic excess discharge of catecholamines may be responsible for lipid, clotting, and cardiovascular abnormalities so frequently found in men exhibiting behavior pattern A, and they discuss several observations that seem to support this hypothesis.

KARPMAN

Goddale, F., Thomas, W. A., and O'Neal, R. M.: Myocardial Infarction in Women. Arch. Path. 69: 599 (June), 1960.

Autopsy material from Washington University, Massachusetts General Hospital, and Radcliffe Infirmary (Oxford, England) from 1940-54 was examined and 13,485 adult autopsies were reviewed. An acute myocardial infarction was defined as having an estimated duration of 1 month or less. Over the age of 50, no statistically significant difference was found between the number of acute myocardial infarctions in men and women (1.02:1). Among the patients less than 50 years of age, a highly significant sex ratio was found (2.87:1 male to female). Of the total number of patients, 10.2 per cent (1,372) had acute myocardial infarctions demonstrated at autopsy. However, only 154 of these occurred in patients under 50 years of age. In addition, at the Washington University, a study of clinical records was made. In the period 1942-1954, of 1,630 patients under the age of 50, 5.4 per cent of the men and 2.5 per cent of the women (2.2:1) had a clinical diagnosis of acute myocardial infarction and died. Among 3,801 patients over the age of 50 who died, 15.4 per cent of men and 14.5 per cent of women had a clinical diagnosis of acute myocardial infarction (1.1:1). A representative sample of the 156,590 patients discharged alive during the period 1942-1954 was taken. Of the patients under 50 years of age, 0.33 per cent had clinically diagnosed acute myocardial infarction (men to women 12:1). Of those patients over 50 years of age, the ratio was 2.4:1, men to women. These data indicate that the autopsy incidence of fatal acute myocardial infarction is now similar in men and women except for the small percentage of infarcts occurring in patients under 50 years of age. This agrees with the data derived from clinical diagnoses of patients dying at the Washington University. However, among those patients discharged alive, acute myocardial infarction was diagnosed clinically in men much more frequently than in women. This finding is perhaps the result of a lack of clinical suspicion of the disease in women, affecting the accuracy of clinical diagnoses in mild cases.

SHEPS

Iliescu, C. C., Kleinerman, L., and Popescu, D.: Consideration on the Short-term Prognosis of Myocardial Infarction. Cor et Vasa 1: 107, 1959.

In 405 patients with myocardial infarction observed by the authors between 1953 and 1958 the mortality during the first 6 to 8 weeks was 20 per cent, regardless of treatment with anticoagulants. In 166 similar observations in 1943 the mortality was 21 per cent. In the presence of hypertension this mortality was 20 per cent in men and 38 per cent in women, while in the presence of diabetes it was 17 and 50, in the presence of previous angina pectonis 21 and 25 per cent and in repeated infarction it was 45 and 33 per cent respectively. At ages of 40 to 59 it was 14 and 32 per cent; at ages of 60-69, 22 and 33 per cent, and at ages of 70-79, it was 37 and 21 per cent respectively.

LEPESCHKIN

Jarvinen, K. A. J.: Physical Activity of Patients after the Onset of Acute Cardiac Infarction. Brit. M. J. 1: 922 (Mar. 26), 1960.

Mortality from acute myocardial infarction is much higher in men than in women. This study reports the physical exertions of 102 men and 31 women immediately after the onset of acute myocardial infarction. Only 28 per cent of the men stopped all physical activity at once or soon after the onset of the attack. The other 72 per cent continued to be active in spite of intense pain, including walking long distances and remaining at work. Most of the women (77 per cent) went to rest immediately at the onset of the attack. These facts may in part explain the difference in mortality in men and women who suffer acute myocardial infarction.

KRAUSE

Kavelman, D. A.: Myocardial Rupture. A Study in Non-Psychotic and Psychotic Patients. Canad. M. A. J. 82: 1105 (May 28), 1960.

Sixteen instances of cardiac rupture were found among 105 patients with myocardial infarction in a series of 1,324 autopsies performed at a military hospital between 1949 and 1958. All patients were men and the average age was 71 years. The rupture involved the left ventricle in each patient; it was anterior in seven, posterior in seven, and in the septum in two. Rupture occurred within 10 days of onset of the infarct

in all except one patient. Two patients had hypertension, and seven were receiving anticoagulant therapy. No evidence was found that exertion following myocardial infarction influenced the tendency to rupture, and the incidence of rupture was nearly the same in psychotic as in nonpsychotic individuals. Rupture occurred four times as commonly among patients who had been in the hospital for a month or less, an observation which was thought to be related not only to the age of the predisposing infarction but possibly also to the better nutritional status of the long-term patients.

ROGERS

Kubicek, F.: Myocardial Infarction with Anomalous Coronary Artery. Ztschr. Kreislaufforsch. **49:** 455 (May), 1960.

A 52-year-old man died with the symptoms of an acute myocardial infarction; the electrocardiogram showed QS deflections and S-T elevations in leads V_1 to V_4, and marked S-T segment depressions in leads II and III. At autopsy it was found that only the anterior descending artery originated from the left coronary artery, which was closed by a fresh thrombus; the left circumflex artery ran behind the aorta and originated from the right coronary artery. A fresh myocardial infarction was transmural in the septal third and subendocardial in the apical two-thirds of the anterior wall.

LEPESCHKIN

Laake, H.: Post-infarction Myocardial Aneurysm. Acta med. scandinav. **167:** 221, 1960.

One hundred and one consecutive patients hospitalized with myocardial infarction during a 5-year period were studied. Three of the 25 patients who died in the hospital and were autopsied were found to have aneurysms. Two of these patients died of cardiac insufficiency and one of ventricular fibrillation. Of the surviving patients (76), five had aneurysms. In all nine cases of aneurysm there was a systolic blowing murmur at the apex and in four there was an early diastolic murmur. Aneurysms developed chiefly in infarcts of the anterior and lateral walls. In two patients the aneurysm was seen in the acute phase of the disease, and in the others the aneurysm developed slowly over an observation period of up to 4 years. The diagnostic measures and surgical treatment are indicated.

SHEPS

Lehmann, H., and Donhardt, A.: Report on Anticoagulant Treatment of Acute Myocardial Infarction. Ztschr. Kreislaufforsch. **49:** 133 (Feb.), 1960.

Of 403 patients with acute myocardial infarction who were treated during the period 1955 to 1957, the total mortality was 29.5 per cent, and the mortality in the first 24 hours was 8.8 per cent. There were 1.4 times as many men as women; the most common age was 51 to 60 in men, 61 to 70 in women. Early death occurred especially in patients with multiple infarction or hypertension, valvular disease, or diabetes. Anterior infarction was more common than posterior, without showing definite differences in mortality; however, involvement of the septum usually resulted in a higher mortality. Two hundred and forty-eight patients were subjected to anticoagulant treatment, while 110 patients were not so treated because of contraindications. The incidence of reinfarction was the same in both groups. The mortality in the first group was 15.4 per cent, in the second group 21.2 per cent. Thromboembolic complications appeared in only 12 per cent of the first group, but in 31.8 per cent of the second group. Myocardial rupture occurred in four patients in each group, on the first through the eighteenth day, and only in anterior infarction. Five patients in the first group experienced extensive gastrointestinal hemorrhage which in two patients lead to death.

LEPESCHKIN

Lenègre, J., Dubost, Ch., and Maurice, P.: A Case of Syphilitic Angina Pectoris, Treated by Surgical Liberation of the Occluded Coronary Ostia. Arch. mal. coeur **53:** 241 (Mar.), 1960.

A 39-year-old man showed typical serologic findings of syphilis, mild aortic regurgitation and angina pectoris of effort, which became so severe that the patient could no longer leave his home. The electrocardiogram showed left ventricular hypertrophy and "strain" with subendocardial injury (marked S-T depression) and probable posterior myocardial infarction (deep Q wave, elevated S-T segment and terminal inversion of the T wave in lead III). Penicillin treatment caused aggravation of angina in spite of cortisone. It was decided to attempt surgical correction of the coronary stenosis under deep hypothermia and extracorporeal circulation. On opening the aorta the right coronary orifice could not be seen, and it could be located only after external dissection of the right coronary artery. The fibrous plaque closing the orifice was perforated and excised, and the fibrous tissue partially obstructing the left coronary orifice was also excised. The aorta was sutured and after re-warming the heart was defibrillated. The total duration of cardiac standstill was 1½ hours. Two months after the operation the S-T depression had disappeared and the patient could

walk rapidly without complaints. Because of the risk involved, the operation is recommended only in severe effort angina of definitely syphilitic origin, after all attempts of medical treatment have failed, and in younger patients in whom coronary arteriosclerosis is unlikely. Even in such cases there is no definite assurance of benefit, as only 70 per cent of patients with syphilitic angina were found to have major ostial coronary stenosis.

LEPESCHKIN

Leonidoff, A. A.: Silent Myocardial Infarction. Dis. Chest. **37:** 561 (May), 1960.

An electrocardiographic survey was carried out on 1,500 patients in a mental institute to determine the incidence of abnormalities and of silent myocardial infarction. Two hundred and three patients showed abnormalities, but only 25 (1.6 per cent) could be called silent myocardial infarctions; the reason for the low incidence of silent myocardial infarction in this series of mentaly disturbed patients was not apparent.

KALMANSOHN

Murai, A.: The Coronary Insufficiency of Neurogenic Origin with Special Reference to Neurocirculatory Asthenia. A Clinical Study by Means of Exercise Electrocardiograms. I. Analysis of Exercise Responses. Japanese Circulation J. **24:** 371 (April), 1960.

An attempt is made here to explain the RS-T and T-wave abnormalities observed in patients with anxiety neurosis or neurocirculatory asthenia. The author believes that the Master two-step test is one of the most sensitive for the study of coronary insufficiency. Four groups of individuals were studied. The first consisted of 10 normal control subjects; the second included 29 patients with neurocirculatory asthenia; the third, 17 patients with neuroses other than neurocirculatory asthenia and closely related diseases; and the fourth, 29 patients with known coronary artery disease. Except for one patient in group II and 12 in group IV, the Master two-step test was performed. Using the criteria of Master, this author found a high incidence of positive tests in the group with neurocirculatory asthenia. The changes noted were not indistinguishable from those found in patients with coronary artery disease. In patients with neuroses other than neurocirculatory asthenia and closely related diseases, positive tests were also encountered, though less frequently than among patients with neurocirculatory asthenia. Since the changes observed in neurocirculatory asthenia were similar to those with coronary disease, it was concluded that in the neurocirculatory asthenia patients coronary insufficiency on exercise was actually present in the absence of coronary artery disease. It was noted that recent work has shown that sympathetic fiber activity may not only cause relative diminution in coronary blood flow due to coronary vasoconstriction, but may also act directly on cardiac metabolism with resultant coronary insufficiency. In patients with autonomic imbalance, therefore, it is suggested that the coronary circulation may possibly be unable to adapt to the abrupt changes of cardiac demands with exercise.

LEVINSON

Murai, A.: The Coronary Insufficiency of Neurogenic Origin with Special Reference to Neurocirculatory Asthenia. A Clinical Study by Means of Exercise Electrocardiograms. II. Correlation between Exercise Responses and Myelographic Findings. Japanese Circulation J. **24:** 387 (Apr.), 1960.

Correlations between the observed exercise responses and the underlying distribution of myelographically suggested subclinical adhesive arachnoiditis were investigated to clarify the possible effect of the spinal sympathetic nervous system on the exercise responses. This study was suggested by animal experiments in which stimulation of the cervical sympathetic fibers resulted in coronary constriction and the fact that changes of positive Master tests had been observed in patients with coronary insufficiency of neurogenic origin. These experiments were carried out on 73 hospitalized patients, none of whom had significant cardiovascular disease. The most consistent finding was a high frequency of subarachnoid adhesions between D_3 and D_6 vertebrae in the ventral aspect of the spinal cord in association with excessive cardio-acceleration after exercise. RS-T depressions occurred in a relatively intimate association to the incidence of the subarachnoid adhesions at upper thoracic levels in both ventral and dorsal aspects of the cord, but this association was not marked enough to be statistically significant. It was concluded that the coronary insufficiency of neurogenic origin was presumably caused, at least in some patients, by the presence of subclinical adhesive arachnoiditis at the upper thoracic levels.

LEVINSON

Papp, C., and Smith, K. S.: Status Anginosus. Brit. Heart J. **22:** 259 (Apr.), 1960.

The authors use the term status anginosus for intractable angina pectoris without evidence of cardiac necrosis. The electrocardiographic pattern is characterized by depression of the R-T segment in two or more leads usually best seen in the

lateral chest leads; the descending limb of the R wave ends well below the P-R segment, continues in a short straight slope downward and then abruptly turns upward to reach the isoelectric level; reciprocal changes are seen in lead aV_R; changes in the posterior leads are rare. Diminution in R voltage may be seen. Thus, these patients show persistently the pattern seen transiently in angina of effort and after the exercise test. Cardiac infarction develops in weeks or months in half of the patients. Postmortem examination of three patients showed subendocardial infarction, infarction of the papillary muscles in two cases and severe arteriosclerotic narrowing of the main coronary arteries.

KALMANSOHN

Robb, G. P., and Marks, H. H.: Evaluation of Type and Degree of Change in Postexercise Electrocardiogram in Detecting Coronary Artery Disease. Proc. Soc. Exper. Biol. & Med. 103: 450 (Mar.), 1960.

An analysis was made of the postexercise electrocardiograms obtained on 922 insurance applicants, most of whom were suspected of having coronary artery disease. The double standard two-step test was employed. Five hundred and nineteen cases were negative. Two hundred and twenty-six subjects had S-T junction depression (more than 0.5 mm.), and 145 demonstrated ischemic S-T segment depression. Among the 145 subjects with ischemic S-T segment depression, the death rate from coronary artery disease was 23.8 or about eight times the rate for S-T junction depression and the negative series. S-T junction depression was apparently a normal response to exercise. In contrast all grades of ischemic S-T segment depression had a high coronary death rate, and this electrocardiographic change was apparently related to coronary insufficiency caused by coronary atherosclerosis. The degree of ischemic S-T depression also correlated well with the severity of the coronary insufficiency.

KRAUSE

Spain, D. M., and Bradess, V. A.: Post Mortem Studies on Coronary Atherosclerosis in One Population Group. Dis. Chest. 36: 397 (Oct.), 1959.

This paper represents part of a continuing postmortem study of coronary atherosclerosis. In the comparison of the degree of coronary atherosclerosis between men engaged in sedentary occupations and those engaged in physically active occupations, over 150 consecutive hearts from cases of sudden death in white men between the ages of 30 and 60 were examined. There appeared to be no significant difference in the degree of coronary involvement based upon occupation. It was also noted that strenuous physical activity or exertion prior to sudden death from acute coronary artery disease did not seem to be a factor of any significant consequence, except in an occasional patient. Similar to Stamler's experimentation with the use of estrogens in chickens, it was shown that in the human being the situation may be the same; that is, estrogens are a factor in the atherogenic process, and there may be a more specific relationship to coronary atherosclerosis than to aortic atherosclerosis. A limited study on a group of suicides indicated that there was no difference in the degree of coronary atherosclerosis from the control group of men who died from accidental death.

MAXWELL

Stamler, J., Lindberg, H. A., Berkson, D. M., Shaffer, A., Miller, W., and Poindexter, A.: Prevalence and Incidence of Coronary Heart Disease in Strata of the Labor Force of a Chicago Industrial Corporation. J. Chron. Dis. 11: 40 (Apr.), 1960.

The medical data on 740 employees of a Chicago corporation were analyzed for a 4-year period, during which time the employees had annual history and physical examinations, chest roentgenograms, electrocardiograms and urinalyses. Of this group 19.4 per cent had hypertension (diastolic blood pressure of 95mm. Hg or above). The incidence of coronary artery disease, rheumatic heart disease, and diabetes mellitus—7 per cent, 2 per cent, and 2 per cent respectively—was in good agreement with results obtained by others in comparable groups. Obesity was associated with a doubling of the risk of developing coronary artery disease, and hypertension with almost a tripling of the risk; the risk of developing coronary artery disease was as great in those with borderline hypertension as in those with severe hypertension; the same relationships of obesity and hypertension existed with myocardial infarction. The incidence of coronary artery disease was twice as great in diabetic patients as in nondiabetic persons. There was a significantly increased incidence of coronary artery disease in the native-born as contrasted with the foreign-born employee, without apparent relationship to their occupational backgrounds.

KALMANSOHN

Svorcik, C., and Spacek, B.: Some Clinical Experiences with Operative "Revascularisation" in Ischaemic Heart Disease. Cor et Vasa 2: 145, 1960.

Nineteen patients with otherwise intractable angina pectoris or cardiac aneurysm leading to heart failure were subjected to cardiomyopexy or aneurysmorrhaphy. Complete or nearly complete freedom from pain resulted in 11 patients, reduction of pain in three, while three patients died following the operation, and one developed hemiplegia. In some patients there was also considerable improvement of the heart failure. Patients with uncontrollable cardiac failure or Bernheim syndrome did not have favorable results and should, therefore, not be subjected to operation; those with fresh myocardial infarction also should not undergo surgery, since they may respond to medical treatment. If, during operation, no myocardial infarction or a strong infarction scar is found, cardiomyopexy should be performed, while if a thin ballooning scar is found aneurysmorrhaphy is the treatment of choice; both methods yielded equally favorable results. Pericardiotomy with sympathectomy was without effect in two of the three patients in whom it was performed.

LEPESCHKIN

Vineberg, A., and Mahanti, B. C.: Evaluation of Experimental Myocardial Revascularization Operations by Ameroid Coronary Artery Constriction. Surgery **47**: 748 (May), 1960.

Ameroid plastic constrictors placed around the origins of the anterior descending and circumflex branches of the left coronary artery in dogs resulted in the death of the majority of animals when 50 per cent or more of the lumina of both branches were simultaneously constricted. The presence of an open septal branch and right coronary artery did not prevent death unless anastomosis between the right and left coronary arteriolar branches occurred. The effectiveness of different revascularization procedures in preventing death and myocardial infarction due to ameroid coronary artery constriction was studied for the following operations: The Beck I operation, cardiopneumopexy with lingular pulmonary artery ligation, cardioaortic Ivalon tube implantation, internal mammary artery implantation, and partial coronary sinus ligation. This was studied in a series of 56 animals, including 10 controls. The hearts of the animals that died or were sacrificed for study were injected with Schlesinger mass and studied by roentgenographic technics. Angiocardiographic studies and histologic examinations of the coronary arteries were also carried out. The only operative procedure that prevented death was internal mammary artery implantation combined with coronary sinus ligation. Seven of 10 animals survived beyond 6 months, and six of these had extensive mammary-coronary anastomoses. One showed intercoronary anastomoses between the left and right coronary arteriolar system of sufficient size to permit the Schlesinger injection mass introduced through the implanted internal mammary artery to fill the left ventricular arteriolar network. The addition of partial coronary sinus ligation seemed to increase long-term survival rate of internal mammary artery implantation when the two major left coronary arteries are very markedly constricted by Ameroid constrictors.

SHEPS

Vineberg, A., Mahanti, B., and Litvak, J.: Experimental Gradual Coronary Artery Constriction by Ameroid Constrictors. Surgery **47**: 765 (May), 1960.

The experimental method for the study of revascularization procedures utilizing the Ameroid constriction method for narrowing and occluding coronary artery vessels is described. Some of the results obtained are discussed. In dogs the critical point of coronary artery narrowing occurred when two major coronary arteries of the left ventricle were reduced by 40 per cent or more. The authors then theorized that when coronary arteriography in man revealed vessels narrowed by 50 per cent or more that such measurements should point to the necessity for corrective coronary artery surgery, especially in the patient under age 55.

SHEPS

Vovsi, M. S., and Kilinskii, E. L.: Studies of the Functional State of the Coronary Circulation. Cor et Vasa **2**: 71, 1960.

Of 46 normal persons submitted to the Master two-step exercise test, none showed a descending S-T depression, an abnormal horizontal depression, an abnormal horizontal depression (exceeding 0.75 mm.), and abnormal ascending depression (exceeding 1 mm. and not related to tachycardia), depression of the T-U junction, or splintering of the QRS complex. Of 89 patients with atherosclerotic angina pectoris and normal resting electrocardiograms, 47 showed a descending or an abnormal horizontal depression, 11 an abnormal ascending depression, 12 depression of the T-U junction, and three splintering of the QRS complex. The abnormal S-T depression appeared only in the precordial leads in 21, only in the limb leads in nine, and in both in 28 cases; it persisted for 1 minute in eight, 2 minutes in 15, 4 to 10 minutes in 29, and 15 to 25 minutes in six patients. Of 44 patients with angioneurotic angina, three showed abnormal horizontal S-T depression, seven abnormal ascending depression, and one T-U depression. The T wave became

inverted in three normal subjects, three patients with atherosclerotic and two with angioneurotic angina, while extrasystoles appeared in three, 11, and two persons of the three groups respectively. The ventricular gradient in the frontal plane was measured in 18 normal persons and 16 patients with angioneurotic angina, where it did not deviate more than 25° from its direction at rest; in 21 patients with arteriosclerotic angina, such a deviation appeared in 11 persons, only two of whom showed abnormal S-T depression. An additional 56 patients with arteriosclerotic angina who had abnormal resting electrocardiograms were subjected to a less severe exercise test; the abnormalities increased in 25 of these and decreased or disappeared in 13; in two the apparent normalization was accompanied by anginal complaints, and was attributed to neutralization of one area of ischemia by another area. In three patients where normalization was not accompanied by angina, it no longer occurred when the test was repeated at a higher work load and could be attributed to actual improvement of the coronary circulation. After 100 to 150 Gm. of glucose by mouth none of the eight normal subjects studied showed S-T depression exceeding 0.5 mm. or isoelectric or negative T waves. These changes appeared in 12 of 18 patients with coronary sclerosis angina, seven of these simultaneously complaining of pain, and in three of seven patients with angioneurotic angina. These changes usually appeared ½ to 1 hour after glucose administration, corresponding to the peak of the blood sugar curve, but in some patients they appeared after 1½ to 2 hours, when blood sugar was returning to normal. In 11 of 17 patients oxygen inhalation was followed by a reversible complete or partial disappearance of these abnormal changes; these were therefore attributed to an increase in myocardial oxygen consumption caused by glucose. In 10 of 12 anginal patients the same changes appeared also after the exercise test. In nine of 29 coronary patients with resting abnormalities, partial or complete normalization occurred after inhalation of nitroglycerin, and in six of these this tendency appeared also after exercise. In 12 of 60 coronary patients nitroglycerin caused appearance or accentuation of the abnormalities, and in nine of these the same behavior was present after exercise. Abnormalities after exercise were prevented or diminished by previous nitroglycerin administration in 11 of 53 coronary patients and accentuated or made to appear in 9 of these patients. The variable response to nitroglycerin was attributed either to dilatation of collateral coronary circulation or to increased coronary insufficiency resulting from hypotension; in the latter case the electrocardiographic response was thus a valuable criterion of whether or not nitroglycerin should be used in a given patient. The nitroglycerin and glucose tests can therefore be used to supplement the exercise test in the diagnosis of latent coronary insufficiency.

LEPESCHKIN

Wilcox, L. D.: Symmetrical Gangrene Associated with Coronary Thrombosis. Canad. M. A. J. **82**: 1066 (May 28), 1960.

Five types of peripheral circulatory failure associated with recent coronary occlusion were described along with brief case histories. The most common type was that of a mural cardiac thrombus embolizing, in 1 patient to the aortic bifurcation producing cold, pulseless legs, and in another to the abdomen and feet. Secondly, hypotension for 4 days following myocardial infarction was attended by pregangrene of the feet of a man in his middle seventies. Whether the latter represented only arteriospasm with deficient blood flow or an additional element of local thrombosis was uncertain. Thirdly, an instance of concomitant terminal aortic thrombosis and probable coronary thrombosis was observed, suggesting the possible existence of a hypercoagulable state as a basis for clot formation in multiple sites. Such a mechanism was also postulated in the fourth type, a patient with erythrocytosis who developed coronary, cerebral, and digital arterial thrombosis with gangrene in the left hand and foot. Finally, a man hospitalized for recurrent coronary failure developed gangrene of all toes within 3 weeks. Autopsy disclosed a recanalized thrombus of at least one digital artery which was thought to have arisen from an atheromatous ulcer of the terminal aorta. Treatment with anticoagulants did not always protect these patients from further arterial occlusions. Arteriography, then corrective surgery were frequently advocated, but the latter was unsuccessful in a single instance. All patients died of the vascular diseases.

ROGERS

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Benchimol, A., Dimond, E. G., and Shen, Y.: Ejection Time in Aortic Stenosis and Mitral Stenosis. Comparison between the Direct and Indirect Arterial Tracing with Special Reference to Pre- and Postoperative Findings. Am. J. Cardiol. **5**: 728 (June), 1960.

Indirect carotid arterial pressure recordings were made photographically from a cup applicator-crystal microphone apparatus. Tracings from 30 normal persons, from 40 patients with moderate or severe mitral stenosis, and from 25 patients with moderate or severe aortic stenosis were studied. In mitral stenosis the only significant abnormality was slight shortening of the total ejection time, which was ascribed to a reduction in cardiac stroke output. After mitral valvulotomy, the ejection time in most instances became normal. In aortic stenosis the ejection time was increased in all patients, the upstroke time was abnormal in 82 per cent, and the ejection angle and time were abnormal in 72 per cent each. After aortic valvulotomy a decrease in ejection time and upstroke time was found in most patients. Comparison showed the indirect carotid recording and the direct aortic pressure pulse to be identical except for a somewhat greater upstroke time in the latter. Four patients with subaortic stenosis were found to have a normal anacrotic limb, prolonged ejection time and a small wave preceding the dicrotic notch. It was suggested that the indirect carotid arterial pressure tracing can give reliable information about the hemodynamics in aortic or mitral stenosis.

ROGERS

Bender, F., and Koch, F.: Reactive Hyperemia as a Means for Improvement of the Indicator Dilution Method in the Diagnosis of Right-to-Left Shunts. Ztschr. Kreislaufforsch. **49**: 129 (Feb.), 1960.

Of 200 patients subjected to dye-dilution tests using dye injection into the cubital vein, 12 per cent showed a notch in the ascending or descending branch of the light absorption curve which was caused by spontaneous changes in the venous return from the arm and simulated the configuration found in right-to-left shunts. These artifacts did not appear if arterial ischemia of the arm was produced by inflating a blood pressure cuff for 4 minutes previous to injection, which was carried out 10 to 15 seconds after deflating the cuff. In some patients with true right-to-left shunt in whom this notch was not visible during ordinary tests because of a very gradual ascent to the summit, such a notch appeared when injection was carried out during reactive hyperemia.

LEPESCHKIN

Beregovich, J., Bleifer, S., Donoso, E., and Grishman, A.: The Vectorcardiogram and Electrocardiogram in Ventricular Septal Defect. Brit. Heart J. **22**: 205 (Apr.), 1960.

Thirty-five patients with proved interventricular septal defects were evaluated from the electrocardiographic and vectorcardiographic standpoint. There were five different electrocardiographic patterns. A normal pattern was seen in 11 patients, seven of whom had a mild interventricular septal defect. Excluding infants, a normal electrocardiogram was invariably associated with a mild defect. Incomplete right bundle-branch block was seen in four patients, two of whom had mild defects, and one of whom had a moderately severe defect. Eleven patients showed evidence of combined ventricular hypertrophy, all of whom had moderate or severe defects. The electrocardiographic diagnosis of left ventricular hypertrophy in the presence of right ventricular hypertrophy was made on the basis of an R wave in V_5 or V_6 of 34 mm. or more, or an R wave of 25 mm. or more when accompanied by a small S wave or S-T depression and T wave inversion. Of the three patients with electrocardiographic evidence of right ventricular hypertrophy, two had associated infundibular stenosis, and one had severe pulmonary hypertension. Clear evidence of left ventricular hypertrophy occurred in only one patient who had associated aortic regurgitation. There were three patterns thought to represent combined ventricular hypertrophy in the vectorcardiogram; in type A the initial segment of the QRS loop in the horizontal plane was directed to the right and anteriorly while the orientation of the rest of the loop was leftward and posterior and the sense of rotation was clockwise; type B was characterized by a large anterior displacement of the QRS loop in the horizontal plane with counterclockwise rotation; type C had a figure-of-eight QRS loop in the horizontal plane with clockwise rotation and a counterclockwise leftward displaced loop in the frontal plane.

KALMANSOHN

NEWS FROM
THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, New York

Telephone Gramercy 7-9170

$1,835,000 Allocated for AHA Grants; Year's Awards to Total $10,000,000

Approximately $1,835,000 has been awarded by the Association in Grants-in-Aid to 233 investigators under its national research program for 1961-62. Previously announced allocations for 179 fellowships total more than $2,000,000. With these awards and those to be made by state and local Heart Associations, the total allocated to research by the Association and its affiliates for the 1961-62 fiscal period will approximate $10,000,000.

The newly announced national grants are for 79 new and 154 continuing studies. Applications for 27 other new grants totaling about $220,000 were approved by the AHA Research Committee but could not be supported for lack of funds in the national research budget. They have been referred to state and local Heart Associations for possible supplementary support, such as many have provided in the past.

A complete list of recipients of new and continued Grants-in-Aid for 1961-62 appears at the end of this section.

Research Applications Ready For AHA Support in 1962

The Association is now accepting applications from research investigators for support of studies to be conducted during the fiscal year beginning July 1, 1962.

September 15, 1961 is the deadline for submitting applications for Research Fellowships and Established Investigatorships.

This also is the final date on which the Association will accept applications for Research Fellowships. In future, state and local Heart Associations will assume responsibility for supporting individuals in this category. Those applying in September may request either one or two-year appointments.

Applications for Grants-in-Aid must be received by November 1, 1961.

Awards will be made as follows:

Established Investigatorships: Usually awarded for five years, subject to annual review, in amounts ranging from $7500-$9900 yearly plus dependency allowances, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. Additionally, a grant of $1000 is made to the investigator's institution for the support of his research program. Applicants for Established Investigatorships may also apply for grants-in-aid to support their research.

Advanced Research Fellowships: Awarded for one or two-year periods to post-doctoral applicants with some research training and experience but who are not clearly qualified to conduct their own independent research. Stipends range from $5500-$6000 annually, plus dependency allowance. During the second year of tenure, they are permitted to spend up to 25 percent of the time in professional and scientific activities not strictly of a research nature, provided that these will contribute to their professional development and do not involve services for a fee. An additional grant of $500 is made to the investigator's department.

Research Fellowships: Awarded on a limited basis to provide training under experi-

enced guidance for young scientists with doctoral degrees. Annual stipends range from $4500 to $7000.

Grants-in-Aid: Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

A limited number of investigators of unusual capacity and widely recognized accomplishment are appointed by the Association as Career Investigators to assure them of financial support throughout their productive lives. These are selected by the Association's Research Committee and *not by application.*

Further information and application forms may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, New York.

Registration Forms Are Ready For AHA Scientific Sessions

Early registration is urged for the 34th annual Scientific Sessions of the American Heart Association, to be held at the Americana Hotel in Bal Harbour, Miami Beach, Florida, October 20-22. Registration forms, which include applications for hotel reservations, are now available from the Association's national office, 44 East 23rd Street, New York 10, New York.

As in the past, this year's program includes six sessions on clinical cardiology. At each of these a panel or symposium and related investigative work will be presented.

In addition, a total of at least 18 special simultaneous sessions will be held throughout the three-day program.

Following is a tentative outline of the Scientific Sessions program:

Friday, October 20: The clinical cardiology sessions include an opening address by Oglesby Paul, M.D., AHA President; the Conner Memorial Lecture, by Clark H. Millikan, M.D., Professor of Neurology, Mayo Clinic; symposia on "Contribution of Phonocardiography to Auscultation," and on "Coronary Arteriography"; a lecture on "Biplane Angiography" by Herbert L. Abrams, M.D., Assistant Professor of Radiology, Stanford Medical Center. Concurrent sessions are scheduled on arteriosclerosis, on biophysical methods in the study of circulation, and on high blood pressure research. Also scheduled is a program for nurses on cardiovascular research as it relates to nursing care of the cardiac patient.

Saturday, October 21: The clinical sessions will include a panel on "Ventricular Arrhythmias"; a lecture on "Closed Chest Cardiac Resuscitation" by James R. Jude, M.D., Johns Hopkins Hospital; the Brown Memorial Lecture on "Physiology of the Peripheral Circulation," by Robert W. Wilkins, M.D., Professor of Medicine, Boston University School of Medicine; and a symposium on "Renal Failure." Simultaneous scientific sessions will be held on basic science, cardiovascular surgery, and on "Compensable Heart Disease, Strain and Trauma."

Cardiovascular Conferences

Scheduled for Saturday evening are "Cardiac Conferences" which will give physicians an opportunity to participate in small group discussions on timely cardiovascular problems. Admission will be by tickets available without charge at registration desks on a first-come, first-served basis.

An open conference on clinical pathology, for which no tickets are required, will be held simultaneously on Saturday evening. It will be moderated by Jesse E. Edwards, M.D., Professor of Pathology, Mayo Foundation, Graduate School, University of Minnesota and Director of Laboratories, Charles T. Miller Hospital, St. Paul. Samuel A. Levine, M.D., Clinical Professor of Medicine Emeritus, Harvard Medical School, and Tinsley R. Harrison, M.D., Professor of Medicine, University of Alabama Medical Center, will discuss the case history, copies of which will be available in advance at the registration desk.

Sunday, October 22: Subjects for the clinical sessions include a symposium on "The Role of Hormones in Heart Failure"; panels on "Ventricular Hypertrophy and Bundle Branch Block" and "Newer Electrocardiographic Lead Systems"; and a lecture on

"ECG Clues Suggesting Myocardial Infarction" by Junior A. Abildskov, M.D., Assistant Professor of Medicine, State University of New York College of Medicine. Concurrent sessions will be held on rheumatic fever and congenital heart disease and on cardiovascular surgery. Cardiovascular films, with introductions and commentary by the author or other authority on the subject, will be shown throughout Sunday.

Meetings Calendar

August 7-10: National Medical Association, New York. John T. Givens, 1108 Church St., Norfolk, Virginia.

August 27-September 1: American Congress of Physical Medicine and Rehabilitation, Cleveland. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Illinois.

September 26-29: American Roentgen Ray Society, Miami Beach. C. A. Good, Mayo Clinic, Rochester, Minnesota.

October 2-6: American College of Surgeons, Chicago. W. E. Adams, 40 East Erie St., Chicago 11, Illinois.

October 3-4: Congress on Occupational Health, Denver. Council on Occupational Health, American Medical Association, 535 N. Dearborn, Chicago 10, Illinois.

October 14-20: International Congress of Neurosurgery, Washington, D.C. Bronson S. Ray, 525 E. 68th Street, New York 21, New York.

October 17-19: International Seminar on Vascular Systems, Miami Beach. John B. Liebler, Heart Association of Greater Miami, 253 S.W. 8th St., Miami 36, Florida.

October 18-20: Council on Arteriosclerosis of the American Heart Association, Bal Harbour, Florida. Jeremiah Stamler, Chicago Board of Health, 54 West Hubbard, Chicago 10, Illinois.

October 20-24: American Heart Association, Annual Meeting and Scientific Sessions (October 20-22), Bal Harbour, Florida. American Heart Association, 44 East 23rd St., New York 10, New York.

October 26-27: The Organization of Bio-Medical Instrumentation and Engineering in Universities and Hospitals, Omaha. Office of Medical Extension, University of Nebraska, Omaha 5, Nebraska.

November 13-17: American Public Health Association, Detroit. Berwyn F. Mattison, 1790 Broadway, New York 19, New York.

November 13-18: Canadian Heart Association and National Heart Foundation of Canada, Annual Meeting and Scientific Sessions, Vancouver. J. B. Armstrong, National Heart Foundation of Canada, 501 Yonge St., Toronto 5, Canada.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

November 27-30: American Medical Association, Clinical Meeting, Denver. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

December 1-2: Symposium on Cinefluorography (3rd) Rochester, New York. Stanley M. Rogoff, University of Rochester Medical Center, Rochester 20, New York.

Abroad

August 22-25: International Pharmacological Meeting (First) Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

August 28-September 2: European Society of Haematology, Vienna. H. Fleischhacker, Wien IX Frankgasse 8, Billrothhaus, Austria.

September 3-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

September 3-10: Inter-American Congress of Radiology, Sao Paulo. W. Bomfim-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-9: International Congress of Angiology, Prague. Prof. Z. Reinis, IVth Medical Clinic, Praha 2/499, Czechoslovakia.

September 6-12: International Congress of Human Genetics, Rome. Luigi Gedda, 5 Piazza Galeno, Rome, Italy.

September 7-9: International Cardiovascular Society Congress (5th), Dublin. H. Haimovici, 715 Park Ave., New York 21, New York.

September 10-15: International Neurological Congress, Rome. G. Alema, Vialo Universita 30, Rome, Italy.

September 11-14: National Congress of Cardiology, San Luis Potosi, Mexico. José M. Torre, Av. V. Carranza No. 2405, San Luis Potosi, S.L.P. Mexico.

1962

October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Secretary General, Ave. Cuauhtemoc 300, Mexico, D. F.

List of 1961-62 Grants-in-Aid Awarded

Recipients of Grants-in-Aid awarded by the American Heart Association for fiscal 1961-62, together with institutions where they will study and subjects of their investigations, are as follows:

New Approved Grants

Beher, William T. Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit. Factors influencing cholesterol metabolism in mammalian tissue.

Blair, Emil. University of Maryland School of Medicine, Baltimore. Physiological, morphological and surgical study of experimental coronary thrombosis and myocardial infarction.

Blumgart, Herrman L. Beth Israel Hospital, Boston. Metabolic aspects of urinary tract infections.

Bowman, Roger. University of Cambridge, England. Normal and fasting metabolism of cardiac muscle and the hormonal influences involved.

Brachfeld, Norman. Cornell University Medical College, New York. Mechanisms of oxygen availability in borderline and fixed flow states.

Bricker, Neal S. Washington University School of Medicine, St. Louis. Ion transport across biologic membranes.

Clarkson, Thomas B. Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina. Atherosclerosis in the pigeon—experimental chemotherapy.

Feinstein, Alvan R. Irvington House, Irvington-on-Hudson, New York. Prevention and sequelae of rheumatic fever.

Finck, Henry. University of Pittsburgh School of Medicine. Muscle cytochemistry.

Fishman, Alfred P. Columbia University College of Physicians and Surgeons, New York. Regulation of the pulmonary circulation.

Friedberg, Felix. Howard University College of Medicine, Washington, D.C. Intracellular proteolytic enzymes (both exo- and endopeptidases) present in heart muscle.

Friedman, Julius J. Indiana University School of Medicine, Indianapolis. Peripherovascular components of tissue blood volume.

Furman, Robert H. Oklahoma Medical Research Institute, Oklahoma City. Influence of sonic forces on serum lipoprotein distribution and on lipid-protein bonds in normal and various hyperlipidemic states.

Gentsch, Thomas O. Yale University School of Medicine, New Haven. Partial perfusion and its application to acute heart failure.

Gergely, John. Retina Foundation, Boston. Physical chemical studies on cardiac actomyosin.

Gilbert, James B. Clayton Foundation Biochemical Institute, University of Texas, Austin. Role and site of binding of the metal ion in metal-containing or metal-activated enzymes.

Glenn, William W. L. Yale University School of Medicine, New Haven. Vascularized cardiac transplants.

Goodkind, M. Jay. Yale University School of Medicine, New Haven. Endocrine effects of myocardial metabolism and ventricular function.

Gould, R. Gordon. Stanford University School of Medicine, Palo Alto, California. Liability of cholesterol in human atherosclerotic lesions.

Greenberg, Wayne V. Medical College of Georgia, Augusta. Mechanism of estrogen induced changes in blood lipids.

Guntheroth, Warren G. University of Washington School of Medicine, Seattle. Role of the respiratory pump in hypoxic spells.

Guze, Lucien B. University of California at Los Angeles School of Medicine. Observations on the association of hypertension and experimental pyelonephritis.

Hansen, Arild E. Children's Hospital of East Bay, Oakland, California. Lipids of blood serum and aorta during childhood.

Haugaard, Niels. University of Pennsylvania School of Medicine, Philadelphia. Functional and biochemical effects of drugs on the myocardium.

Heimberg, Murray. Vanderbilt University School of Medicine, Nashville, Tennessee. Hormonal control of lipid metabolism.

Henly, Walter S. Baylor University College of Medicine, Houston. Surgical correction of mitral insufficiency by means of intracardiac synthetic prostheses.

Hickam, John B., and *Manfredi, Felice.* Veterans Administration Hospital, Indianapolis. Treatment of acute respiratory acidosis with extracorporeal circulation.

Irwin, John W. Massachusetts Eye and Ear Infirmary, Boston. Hemodynamics of the microvascular system.

Jacobs, Earl E. Stanford University School of Medicine, Palo Alto, California. Characterization of phosphorylation coupled to electron transport processes in cytochrom oxidase.

Kaplan, Samuel. Children's Hospital, Cincinnati. Adaptation of the circulation in the newborn.

Katz, Joseph. Cedars of Lebanon Hospital, Los Angeles. Intermediate metabolism of lactating mammary gland.

Katz, Louis N. Michael Reese Hospital and Medical Center, Chicago. Cardiac, metabolic and hemodynamic interrelationships.

Keys, Ancel and *Grande, Francisco.* University of Minnesota School of Public Health, Minneapolis. Influence of dietary fat and dietary cholesterol on serum cholesterol concentration in man.

King, Tsoo E. Oregon State College, Corvallis. Cellular respiration in heart muscle.

Knoefel, Peter K. and *Huang, K. C.* University of Louisville School of Medicine. Flux movement of organic acids in kidney cells.

Krayer, Otto. Harvard Medical School, Boston. Action of guanethidine upon the mammalian heart.

LaBella, Frank S. University of Manitoba Faculty of Medicine, Winnipeg, Canada. Anterior and posterior pituitary hormones; formation, secretion and action on connective tissue.

Levitin, Howard. Yale University School of Medicine, New Haven. Concentrating and diluting functions of the kidney.

Levy, Robert S. University of Louisville School of Medicine. Purification and characterization of lipoprotein lipase from tissue and plasma, and its variations in plasma during abnormal conditions of lipid metabolism.

Libelt, Robert A. Baylor University College of Medicine, Houston. Effect of the adrenal gland on obesity in mice.

Love, William D. Tulane University School of Medicine, New Orleans. Measurement of regional blood flow by external isotope techniques.

Maffly, Roy H. University of California School of Medicine, San Francisco. Coupling of metabolic energy and active sodium transport.

Martin, Ralf and *Nelson, Clifford V.* Maine Medical Center, Portland. Quantitation of the heart vector.

Miller, Tracy B. State University of New York Upstate Medical Center, Syracuse. Action of antidiuretic hormone.

Milnor, William R. Johns Hopkins University School of Medicine, Baltimore. Pulmonary vascular distensibility in man.

Montgomery, Hugh. University of Pennsylvania School of Medicine, Philadelphia. Measurement of absolute oxygen tension in intact living tissues, with special reference to human muscle.

Moore, Carl V., and *Perry, H. Mitchell, Jr.* Washington University School of Medicine, St. Louis. Pathogenesis and treatment of hypertension and atherosclerosis.

Moulder, Peter V. University of Chicago School of Medicine. Biochemical and physiologic studies on explanted and transplanted canine hearts.

Mueller, Helmut. University of Pittsburgh Graduate School of Public Health. Enzymatically active fragments of the meromyosins.

Nathan, Paul. May Institute for Medical Research, Jewish Hospital Association, Cincinnati. Survival of transplanted rat kidneys after intravenous injection of antigen.

Porter, John W. University of Wisconsin Medical School, Madison. Mechanism of the enzymatic synthesis of fatty acids.

Rammelkamp, Charles H. Western Reserve University School of Medicine, Cleveland. Controlled studies of effects of intensive penicillin therapy on the development of valvular heart disease in patients with acute rheumatic fever.

Rector, Floyd C., Jr. University of Texas Southwestern Medical School, Dallas. Mechanism of bicarbonate reabsorption by the kidney.

Regan, Timothy J. Seton Hall College of Medicine, Jersey City, New Jersey. Metabolic basis of ion transport in the heart and relationship to its functional properties.

Relman, Arnold S. Massachusetts Memorial Hospitals, Boston. Role of free amino acids in the regulation of potassium metabolism in health and disease.

Rogers, Lloyd S. State University of New York Upstate Medical Center, Syracuse. Electropolarographic studies of myocardial oxygenation; evaluation of cardiac revascularization procedures.

Rubin, Albert L. Second (Cornell) Medical Division, Bellevue Hospital, New York. Metabolic alterations in the uremic syndrome.

Rudolph, Abraham M. Albert Einstein College of Medicine of Yeshiva University, New York. Pulmonary hypertension and pulmonary vascular disease.

Sawyer, Philip N. State University of New York Downstate Medical Center, Brooklyn. Mechanism of ion transport across blood vessel wall.

Siegel, Alan C. Children's Memorial Hospital, Chicago. Group A streptococcal infections in children.

Soroff, Harry S. New England Center Hospital, Boston. I. Metabolic and hemodynamic effects of assisted circulation. II. Development of partial and complete prostheses for replacement of diseased aortic and mitral valves.

Spiro, Robert G. Baker Clinic Research Laboratory, Boston. Structure and metabolism of glycoproteins.

Spitzer, John J. Hahnemann Medical College, Philadelphia. Fatty acids removed *in vivo* by heart, liver and muscle.

Stetson, Chandler A. and *Lazzarini-Robertson, Abel, Jr.* New York University Post-Graduate Medical School, New York. Metabolic and immunological changes occurring in transplanted tissues.

Swan, Henry. University of Colorado Medical Center, Denver. Physiological and technical studies related to cardiovascular surgery.

Taylor, C. Bruce. Evanston Hospital Association, Evanston, Indiana. Human cholesterol metabolism and its relationship to atherosclerosis.

Taylor, Henry L. University of Minnesota School of Public Health, Minneapolis. Prolonged pulse recording of free living men.

Taussig, Helen B. Johns Hopkins University School of Medicine, Baltimore. Etiology of congenital malformations of the heart and great vessels.

Thompson, W. T., Jr. and *Said, Sami I.* Medical College of Virginia, Richmond. Gas exchange and the pulmonary capillary circulation.

Van Breemen, V. L. Mercy Institute for Biomedical Research, Denver. Electron microscopy of normal and experimentally altered cardiac muscle.

Wannamaker, Lewis W. and *Ayoub, Elia M.* University of Minnesota Medical School, Minneapolis.

Fate of streptococcal cell components following phagocytosis.

Warner, Homer R. Latter-day Saints Hospital, Salt Lake City. Development of methods for calculating flow from pressure in the aorta.

Webb, J. Leyden. University of Southern California School of Medicine, Los Angeles. Actions of cardio-active drugs on the membrane potentials and contractility of atrium.

Weissler, Arnold M. University of Texas Medical Branch, Galveston. Ventricular function in congestive heart failure.

Welsh, Richard S. University of Redlands, Redlands, California. Characterization of undegraded, nonfibrous forms of desoxyribonucleoprotein and desoxyribose nucleic acid from calf thymus nuclei.

Wessler, Stanford. Beth Israel Hospital, Boston. Experimental thrombolysis.

Wesson, Laurence G., Jr. New York University School of Medicine, New York. Diurnal cycle of renal function and electrolyte excretion in human essential hypertension.

Wexler, Bernard C. May Institute for Medical Research, Jewish Hospital Association, Cincinnati. Arteriosclerosis in the rat.

Williams, Clyde M. University of Florida College of Medicine, Gainesville. Aromatic amine metabolism in essential hypertension and pheochromocytoma.

Wilson, John L. American University of Beirut School of Medicine, Beirut, Lebanon. Congenital and acquired heart disease in the Middle East.

Wood, Earl H. Mayo Association, Rochester, Minnesota. Upstream sampling indicator-dilution method for detection and quantitation of valvular regurgitation.

Woodbury, Robert A. University of Tennessee College of Medicine, Memphis. Basic mechanism contributing to angina pectoris.

Zugibe, Frederick T. University of Pittsburgh School of Medicine. Development of a standard method for determining the degree of coronary atherosclerosis at autopsy utilizing a plastic injection technic.

Continued Grants

Acheson, George H. University of Cincinnati College of Medicine. Dihydrogenated cardiac glycosides.

Alexander, Natalie. University of Southern California School of Medicine, Los Angeles. Observations and experimental studies on rabbits with inherited hypertension.

Ambrus, Julian L. Roswell Park Memorial Institute University of Buffalo, Buffalo, New York. Fibrinolysin system.

Bing, Richard J. Wayne State University College of Medicine, Detroit. Cardiac metabolism.

Bohr, David F. University of Michigan Medical School, Ann Arbor. Determinants of non-neurogenic vascular tone in normal and hypertensive animals.

Bondurant, Stuart. Indiana University School of Medicine, Indianapolis. Effect of central vascular engorgement on true pulmonary compliance.

Brady, Allan J. University of California at Los Angeles School of Medicine. Link between excitation and contraction.

Brown, David F. Albany Medical College, Albany, New York. Role of triglyceride metabolism in ischemic heart disease.

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